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THESIS FOR THE DEGREE OF M.D.

on

INVESTIGATIONS ON THE ACTION AND USES  
OF VASO DILATOR SUBSTANCES IN  
HIGH BLOOD PRESSURE

by

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INVESTIGATIONS ON THE ACTION AND USES OF  
VASO-DILATOR SUBSTANCES IN HIGH BLOOD PRESSURE.

INTRODUCTORY.

Methods of accurate observation on human blood pressure are of recent invention and use. Digital examination of the pulse, physical examination for the presence of an hypertrophied left ventricle and accentuation of the aortic second sound, together with sphygmographic records with the Marey or the Dudgeon apparatus have in the past led us to our conclusions regarding the conditions under which the heart is working and of the resistance in the arterioles and capillaries to the circulating blood. So far as it goes the information conveyed is of great clinical value particularly in the hands of trained observers. These Clinical methods we still have at our disposal, but unquestionably they leave us ignorant in many cases of a great deal that is taking place in the Cardio vascular system.

The idea of instrumental measurement of blood pressure has been long entertained, and practised for years with crude instruments, whose results could not be accepted as scientifically correct.

For years Burdon Sanderson, Mahomed, Huchard,  
Clifford/

Clifford Allbutt and others worked at blood pressure with imperfect instruments. Their foundations at any rate solved the principles that regulate accurate blood pressure estimations, and now we have evolved from these beginnings instruments for which the greatest accuracy can be claimed, and as an addition to our physical examination we are now in many cases able to come much closer to the actual conditions under which the blood circulates and is controlled.

Many instruments are on the market at the present time and undoubtedly the most satisfactory is Erlangers - recording the blood pressure graphically. It is, however, too elaborate and bulky for every day use. Of the simpler and smaller forms one of the best is the Riva Rocci sphygmomanometer with the broad Recklinghausen cuff. Its two modifications by Dr. Lockhart Mummery and by Dr. Martin are also trustworthy. We have also two instruments by Dr. Oliver with a spirit index in the manometer instead of mercury as all the other instruments have. Dr. George Gibson has also invented a very accurate apparatus, but like Erlangers it is not suitable for every day bedside use.

Many others might be mentioned but these are the most serviceable and accurate.

The/

The principle in all methods of estimating blood pressure is the same, viz. to balance the blood pressure by air compression, the latter being measured at the same time on a scale in millimetres of mercury. A broad cuff - and the broader the cuff the less the possible error in the estimation - encircles the upperarm or forearm. The inner surface of the cuff is covered by a rubber lining stitched to the margins of the cuff into which air is driven through a tube from a hand ball. The hand ball is also connected by another tube with a manometer the scale of which measures in millimetres of mercury the amount of compression.

In my observations on blood pressure in general and in the particular observations that form the subject of this thesis I have thoroughly tested most of the instruments in use, in order to obtain as great a degree of accuracy as is possible. I have employed the instruments already mentioned except Erlanger's, and have found the figures fairly uniform in the same cases - the manometers with the spirit index (Oliver's) giving a slightly higher reading than the mercury instruments to the extent of between 5 and 10 millimetres.

By means of these instruments two main facts are obtained/



obtained or two pressures can be measured both of which are of immense value.

These are the systolic or maximal blood pressure and the diastolic or minimal pressure.

1. THE SYSTOLIC OR MAXIMAL PRESSURE.

The systolic blood pressure is estimated most conveniently in the upper arm or forearm. Between these two measurements I have never been able to find any appreciable difference. The cuff or armlet is buckled on the arm and the tubes from the rubber ball are connected one with the armlet and the other with the manometer. Air is gradually pumped into both, and at the same time the fingers of the left hand observe the radial pulse. At a certain point when the air pressure in the cuff is sufficient the radial pulse stops. A little air is then allowed slowly to escape by turning a screw close to the hand ball, until the pulse at the wrist is again just felt to beat. When the radial pulse has returned the height of the column of mercury is read off on the scale. This figure gives the systolic or maximal pressure.

2. THE DIASTOLIC OR MINIMAL PRESSURE is obtained in a different way and for it I much prefer the spirit index instruments of Dr. Oliver. As the air is/

is pumped into the armlet and manometer, the indicator (mercury or spirit) begins to oscillate with each pulse beat. As more air is pumped in and the index rises, the oscillations become gradually greater until a maximum is reached after which they become less. The diastolic pressure corresponds on the scale to the level at which the maximum oscillations are observed.

Both systolic and diastolic pressures convey useful and instructive information. The systolic pressure represents approximately the intra-ventricular pressure, while the diastolic measures the sum of all the factors of resistance to outflow through the arterioles viz. viscosity of the blood, arterial friction, total arteriole cross section at the given instant.

The diastolic or minimal pressure is practically constant throughout the whole arterial system, while the systolic falls gradually as the arteries become smaller, and in the arterioles the two pressures closely approximate each other.

#### NORMAL BLOOD PRESSURE AND HIGH BLOOD PRESSURE.

Before detailing the investigations I have made with vaso dilators in conditions of high blood pressure it will be suitable to summarise

1. normal blood pressure,
2. high blood pressure - what it is,  
what are the conditions that lead to its  
production, and the various forms in which it may  
manifest itself.

#### NORMAL BLOOD PRESSURE.

Many thousand observations have been made in healthy individuals at all ages to ascertain as nearly as possible the normal blood pressure standard. It is now generally agreed that the normal systolic pressure in a healthy adult under 50 is about 120 to 125 m.m. of Mercury, and the diastolic or minimal pressure about 90 millimetres of Mercury. The pulse pressure is therefore about 30 millimetres - equal to one quarter of the maximal pressure. I am, however, - from observations over hundreds of cases - inclined to the opinion that, even with strict precautions as to the time of day, relationship to meals, and with the individual in a horizontal position, we must allow a greater range of figure for the normal systolic pressure and would give 100 m.m. to 135 m.m. as fairly representing its limits, and 90 m.m. to 105 millimetres for the diastolic pressure.

In women the pressures are about 10 per cent less than/

less than in men. If, in addition, we take into account Physiological variations that are daily and hourly occurring such as exercise, diet, emotional excitement etc., the range of normal pressure must be further extended and I would accept Oliver's figures as wide enough to include all possible Physiological variations. They are 90 to 145 millimetres of mercury for the systolic pressure and 80 to 115 millimetres for the Diastolic pressure. *Records* above or below these figures raise at once a suspicion of some causal factor other than Physiological.

#### CONDITIONS OF HIGH BLOOD PRESSURE.

##### Pressure rise with age.

To avoid needless repetition I shall in future refer always to only one of the Pressures, viz. the systolic. Their rise and fall do not go always hand in hand, but it is elevation of systolic pressure that I have worked with principally. In a healthy adult then under 50 years of age a pressure above 145 becomes pathological. After 50 years of age there is a tendency for a gradual rise to take place in the blood pressure, rising, say, from 130 in an individual to 135 or 140, and if at 60 or 65 years of age it does not exceed the latter figure it may be regarded as normal for that particular age. This gradual increase is due to changes that take place/

place chiefly peripherally in the vascular system, viz. increased resistance and diminished elasticity in the arteries. This calls for further work from the heart and hence the rise in pressure. The increase in pressure in these cases one might almost call natural or involuntary.

#### TEMPORARY ELEVATIONS OF BLOOD PRESSURE.

A rise in blood pressure may be temporary - either temporary rises above a normal pressure, or temporary increases in a pressure already high.

In the former category we have elevated pressure that occurs with intense excitement or undue exertion (e.g.) during labour pains with compression of the abdominal walls, or reflex rises from acute pain of any sort, (eg) biliary colic or the beginning of acute peritonitis, or reflex rises from peripheral influences. These are comparatively unimportant.

#### ACTION OF DRUGS AND EXTRACTS.

We know also that various drugs, such as digitalis, caffeine, nicotin, and animal extracts such as adrenalin produce an increased blood pressure. These however are only apparent during the exhibition of the particular substance.

PHYSIOLOGICAL EXPERIMENTS.

PATHOLOGICAL HYPERTENSION.

It is in the realm of disease, however, that we find innumerable examples of increased blood pressure. It varies in degree within wide limits. Anything from 150 millimetres of Hg. to 300 m.m and over is found in the various pathological conditions. A large amount of work has been done in attempts to estimate in all conditions the corresponding blood pressure. We have very few records of pressures over 300 m.m of Hg. and this figure is only reached in cases of cerebral compression and haemorrhage. In the great run of cases with high blood pressure the readings range from 200 m.m. to 260 millimetres of mercury, and in the lesser degrees from 160 m.m. to 200 m.m.

HIGH BLOOD PRESSURE IN CHRONIC BRIGHTS DISEASE.

Without actual estimation, the existence of high blood pressure was first of all recognised in certain forms of Bright's Disease. In the chronic forms it was observed that a sequel or concomitant of the kidney condition was an hypertrophied left ventricle and a pulse of high tension. The exact relationship between these three factors, kidney, heart, and vessels in Bright's Disease has been long and ably argued since the writings of Gall, Sutton and Johnston, but it is not necessary here to enter into that./



that. Suffice it to say that it is now generally agreed and always found that, in the chronic forms of Bright's disease, we have the most constant and one of the most marked examples of high blood pressure.

But elevation of blood pressure occurs apart from nephritis in a considerable number of cases. Of the various factors that go to make up the vascular apparatus and maintain the pressure at a level necessary for its economy the arterioles and capillaries are undoubtedly the most important. And further, the changes that take place in these vessels are mainly responsible for the pressure variations in disease. It is well known that from various causes pathological changes take place in the larger arteries, middle sized, and smaller arteries, of the nature of hardening or sclerosis of the walls - changes known as atheroma, arteriosclerosis and endarteritis. So far as the blood pressure is concerned the result is the same and therefore I will employ the word arteriosclerosis as including all changes in vessel walls and meaning any thickening or hardening of that wall.

#### RELATIONSHIP BETWEEN ARTERIO SCLEROSIS AND HIGH BLOOD PRESSURE.

Within recent years a vast amount of discussion has/



has taken place as to the exact relationship between arterio sclerosis and high blood pressure. For a time following Von Basch - whose opinions have evidently been widely directly copied by the writers who succeeded him - it was maintained that arterio-sclerosis arising from whatever cause produces gradually and directly an increased blood pressure, and is the chief cause of this increase. About 1894, however, Huchard and Clifford Allbutt independently showed that arteriosclerosis is rather a consequence than a cause of increased blood pressure. This was a marked advance and is the foundation of all our system of blood pressure knowledge. They expressed the opinion that in arterio sclerosis we have a mechanical condition arising from excessive blood pressure - the degeneration of the arteries arising from overstretching.

This does not in my opinion express the whole truth, for in many we have evident and palpable signs of arterio sclerosis in the peripheral arteries without undue elevation of blood pressure.

However, it is undoubtedly a mistake to employ arterio sclerosis and high blood pressure as synonymous terms, and as great a mistake to look on arterio sclerosis as a disease. It is a pathological/

pathological result and as such only should the term be used. Many conditions may and do result in arteriosclerosis - using the word in its widest and most literal sense. We have arteriosclerosis from chronic renal disease, from continued and excessive muscular exertion, from increased blood pressure from whatever cause, from gout, alcohol, syphilis, lead poisoning, and following the poisons of typhoid, tubercle, pneumococcus, staphylococcus, and streptococcus. From the clinical standpoint and in relation to treatment the most important form is undoubtedly that following increased blood pressure.

The exact relationship between this form of arteriosclerosis and blood pressure I would from my investigations summarise in the following propositions.

1. High blood pressure exists in many cases without evident arteriosclerosis in the palpable arteries, and with no evidence of nephritis in any form.
2. In most of these cases arteriosclerosis follows after varying periods, usually in from 4 to 5 years if untreated.
3. Arteriosclerosis may be present in the peripheral arteries (e.g.) radial, and yet the blood pressure is not raised. The recognition of Proposition 1 marked

a/

a distinct advance in our knowledge both of arteriosclerosis and of high blood pressure. It not only clears up many uncertainties of diagnosis but holds out great hope of cure in cases that formerly had been allowed to progressively advance.

#### HIGH BLOOD PRESSURE WITHOUT EVIDENT ARTERIOSCLEROSIS

Such cases of elevated blood pressure without arteriosclerosis are not rare if sought for. They can, however, be detected only by the sphygmomanometer as in most if not all symptoms are only slight and vague at the onset. In some of these cases discovered accidentally to have high pressure - the patient will insist that he or she never felt better, accounted for probably by the increased blood supply to the brain, as a result of the raised blood pressure. These important cases of high blood pressure in its early stages one does not readily meet among Hospital patients. By them treatment is never sought in the early stages but only later after arteriosclerosis has set in and has advanced.

They are most likely to be met with among the well to do where treatment is sought for ailments and symptoms slight in themselves.

During/

During the past two years I have had the opportunity of seeing eight of these cases. As I have indicated is usually the case they were all in very good health and came under observation for some trifling ailment. Three complained of slight headaches, three had trouble with their eyes of the nature of vague pains suggestive of glaucoma and two had sought the advice of an oculist for a sudden partial loss of vision in one eye.

One of these cases will give a better idea of this important type of high blood pressure.

Miss M. aged 49 had to see an oculist for pains in her eyes and seeing halos. Except for these she said she was quite well. I was asked to examine her generally. I found that all the systems were healthy or very nearly so. The heart was not enlarged, and there were no murmurs. The aortic second sound was very slightly accentuated. The pulse was 70 per minute, and tension was somewhat raised. The vessel walls - radial and brachial - showed no signs of thickening.

The urine contained no albumen.

It had been tested previously and often and albumen was never found. The other systems were healthy.

The/

The blood pressure was considerably raised. Estimated by Oliver's instrument and then by Erlanger's the systolic pressure was 190 millimetres of mercury and the diastolic 150 millimetres. This elevation of pressure was all that could be found.

This case represents the very earliest stages of high blood pressure; and it is rare to come across them so early. After the increased blood pressure has operated for some time symptoms soon begin to show themselves. Accentuation of the aortic second sound, I have found the first definite objective sign in these cases, and I would suggest <sup>that</sup> in every case ~~where there is~~ even a suspiciously accentuated second aortic sound, a blood pressure examination should be made. Following on this, symptoms referable to the heart - pain, dyspnoea, etc. - or ~~to the stomach~~ or liver or other organ manifest themselves. With the onset of these latter symptoms one will usually find that now arteriosclerosis of the peripheral arteries has set in. This gradually increases and becomes general in all the arteries. (In these cases it is of course essential to eliminate one of the forms of chronic Bright's disease for in them the combination of hypertension and arteriosclerosis is constant). In an average case the arteriosclerosis usually/

usually develops and is present in the peripheral arteries in three or four years, though I have found it sooner.

From a therapeutic point of view these presclerotic cases - as one might call them - are all important for by proper treatment one can hold out the hope if not of cure, at any rate of a possibility of delaying the advance of the sclerotic process for a considerable time.

#### CAUSE OF THE HIGH PRESSURE IN THESE CASES.

The actual cause of this idiopathic elevation of blood pressure is as yet not definitely known, and the various suppositions and arguments are too lengthy to detail here. It may be said shortly, however, that the rise of pressure is undoubtedly a necessary one if the affected individual is to have a requisite blood flow in all the capillary areas of the body. Increased resistance is present somewhere, due it may be to increased viscosity of the blood, or presence in the blood of toxins from the alimentary canal, extracts of animal tissues or excretory substances etc.

Now the normal average blood pressure is maintained with great constancy. The various regulating/



regulating mechanisms so bring it about that the local necessities of large areas are supplied with the least variations of pressures. Much work has been done clearing up the mechanism of normal blood pressure maintenance. Hasenfeld and Hirsch have proved by experiments that a rise in blood pressure is normally overcome by dilatation of the countless arterioles in the abdominal viscera evoked by the depressor nerve, and that an abnormally high blood pressure cannot exist permanently unless there be some damage to the regulating power of the visceral circulation. They also proved that arteriosclerosis leads to hypertrophy of <sup>the</sup> left ventricle only when the splanchnic areas are diseased, and that arteriosclerosis of peripheral arteries does not appear to have this influence on the circulation. This latter point is corroborated clinically and stated in proposition 3 for we do find many cases of marked arteriosclerosis and yet no elevation of blood pressure.

evident arteriosclerosis

In these cases then of hypertension without  $\wedge$  it is probable from their observations that, though it cannot be detected clinically, there is already a commencing sclerosis of the arterioles of the splanchnic area to account for the elevated blood pressures.

And/



And this advancing contraction of central arterioles demands for its over-coming for the vascular economy a raised and gradually rising blood pressure.

THE ACTION AND USES OF VASO-DILATORS SUBSTANCES  
IN CONDITIONS OF HIGH BLOOD PRESSURE.

In the conditions of high blood pressure that I have briefly summarised we have recourse to various remedies and prophylactic measures. The indication undoubtedly is to obtain such an amelioration of the individual's condition as shall result in a reduced blood pressure or to adopt means that shall prevent its progressive increase. These aims can be encouraged and reached by many measures, including attention to diet, exercise, mode of living etc. We have at our disposal, too, many drugs that from observation and experience have been found of benefit in these conditions.

For the past two years I have, in Leith Hospital, been engaged in investigations on abnormal blood pressure and in addition have made a large series of observations with various substances to ascertain, if possible, their action and benefits or otherwise in the numerous cases of hypertension that have come under observation. Of these substances the best known are the various nitrites and organic nitrates. For long their/

their vaso dilator action has been known and therapeutically employed. Their action has been investigated physiologically on animals, and clinically by observations on the pulse, by the finger' and the sphygmograph. These methods undoubtedly convey a considerable amount of information, but it cannot be maintained that the information so gleaned is comparable in exactness and comprehension to ~~exact~~ blood pressure readings. Something definite is conveyed to the mind by ~~exact~~ numbers, and the knowledge that a blood pressure measures 190 millimetres of mercury is more exact and satisfying than a report that the pulse tension is "slightly" or "moderately" or "markedly" increased. So far as I am aware this has not been done and my purpose has been, if possible, by actual sphygmo-manometric observations to exactly determine the individual and relative actions and uses of the various nitrites and other substances in conditions of high blood pressure.

Much work has been done clinically and experimentally on the various nitrites. Cash investigated their action and was able to definitely group them as regards promptness and lasting effect, and clinically several of them became used through the/

the writings of Brunton and others - particularly amyl nitrite and nitro-glycerine. It was then found that though producing a very speedy and powerful action, their evanescent nature militated against their having more than a very limited use.

Numerous observers then undertook a series of investigations to obtain, if possible, a substance having a less powerful but more prolonged action. Matthew Hay experimented with ethyl nitrate and allied bodies but concluded they were of no practical use. Leech investigated the nitrates of the fatty series and found all possessed dilating effects on the blood vessels - generally of a prolonged kind. He suggested their use clinically but found they were liable to cause headaches. Lauder Brunton tried hydroxylamine hydrochlorate. It answered the purpose, but he found it liable to cause gastric disturbance.

Bradbury, from the higher valent alcohols, was able to produce and investigate a series of nitro bodies. These were methyl nitrate, Glycol (ethylene) Dinitrate, Glycerol Trinitrate (nitroglycerine), Erythrol Tetranitrate and Mannitol Hexanitrate.

Their activities he found varied within wide limits due naturally to their different solubilities and liability to decomposition. Methyl nitrate he found/

found the most soluble but with a comparatively slight vaso motor action. Glycol dinitrate had a powerful action resembling that of nitroglycerine. Erythrol and Mannitol are less soluble, have a weaker effect as vaso dilators, but their action is more prolonged. He recommended their use as likely to fulfil all requirements where more prolonged action was desirable than could be obtained by nitroglycerine.

The action of these nitrates he ascertained by perfusion observations on animals and by sphygmographic findings in man. His conclusions I will refer to when I have detailed my results obtained by blood pressure measurements.

I have confined my observations to the nitrites and nitrates that are in general therapeutic use viz. Nitroglycerine and liquor trinitrini, sodium nitrite, Potassium nitrite, erythrol tetranitrate, mannitol hexanitrate, and cobalto nitrite of Potassium.

With the finger and by the sphygmograph one can obtain only a general idea of the action of these bodies on blood pressure. We find that the pulse becomes softer to the finger, that the characteristics of the beat become altered and that these changes last a certain time. With blood pressure measurements one can obtain a much more complete knowledge of/

and  
of how these bodies act, in actual figures the  
exact effect they have on the blood pressure.

In my investigations I have analysed their  
action in conditions of high blood pressure under  
the following heads.

1. The time the action begins after administration  
of the nitrite.
2. The amount of reduction in the blood pressure  
produced by a single dose and in repeated doses.
3. The time in which the maximum action is attained.
4. The time in which the action of the nitrite  
begins to pass off.
5. The time in which the blood pressure again  
regains its normal level.

These points I have attempted to ascertain  
for the various nitrites mentioned and other  
supposed vaso dilators, and from them it will be  
possible to summarise the action of the individual  
nitrites and to make a comparison of their relative  
vaso dilating effect.

Further the dosage of the various nitrites in the  
cases of abnormal blood pressure in which they may  
be employed will be discussed.

And finally one can decide the various conditions  
of hypertension in which they will be beneficial and  
those in which they should not be employed.

## METHODS OF OBSERVATION AND INVESTIGATION.

My observations with the various nitrites will be detailed only in so far as I have used them in abnormally high blood pressure. I have had the opportunity of studying many cases of this condition in its various types in the out patient Department and in the wards of Leith Hospital. The cases in <sup>were mostly under the charge</sup> the wards of Drs. Elder and Langwill to whom I am indebted, during the past two years, for the privilege of making my blood pressure estimations.

## INSTRUMENTS EMPLOYED.

The instruments I used were the Lockhart Mummery and the Martin modifications of the Riva Rocci apparatus, <sup>and</sup> Dr. Oliver's two instruments, most of <sup>the observations</sup> being made with the Armlet of Dr. Oliver's new instrument and the manometer from the Lockhart Mummery apparatus.

At the outset I do not differentiate the various types of high blood pressure in which I employed the nitrites as I wish to indicate their action in hypertension no matter what the cause.

My observations were all made with the patient in bed lying on the back. They were all convalescent from the condition for which they had been admitted or/



or suffered from some chronic ailment.

#### TIME OF OBSERVATION.

It is essential that blood pressure observations should always be made if possible at the same time of day, and, in addition, at a time in the day at which we know the pressure to be more or less constant.

In this way only it is possible to avoid any error that might arise from variations in pressure we know take place at different periods of the day. For this purpose I chose the hours between 10 a.m. and 1 p.m., for I found, and others have found the same, that between these hours the pressure remains constant and no allowance requires to be made for natural variations. This was essential, as an observation, particularly in the case of the longer acting nitrites, lasted for several hours.

These hours were convenient for another reason in that the nitrites were given on a more or less empty stomach, and there was no question of the observation being nullified by delayed absorption or by changes in the blood pressure following a meal.

#### METHOD OF OBSERVATION.

For several days before making an observation I estimated the blood pressure of the individual to accustom him to the process and so avoid the rise in/  
in/



in pressure that occurs in those who are unaccustomed to the idea of the air compression of the arm and whose mental condition is one of perturbation at the whole process.

On the day of administration of the nitrite I always first of all estimated the blood pressure three or four times at short intervals, as in such observations with nitrites it is of primary importance to ascertain precisely the actual pressure before administration. I then waited for a few minutes, administered the nitrite, and noted the time of administration.

At fixed and successive intervals the pressure was taken and noted down and this was continued for varying periods until the effect of the nitrite had passed off or nearly so. The fall in blood pressure after administration of a nitrite one might estimate by taking

1. the digital pressure<sup>and</sup> estimating the rise that follows the administration of a nitrite.
2. The diastolic brachial pressure and observing the fall.
3. The systolic brachial pressure and observing the fall.

With the instruments I employed the greatest ease and accuracy is obtained by working with the systolic/

systolic pressure and this method I employed in all my observations.

NITRITES AND NITRATES EMPLOYED.

1. Tabloids of Nitro glycerine and solution of liquor trinitrini.
2. Solution of sodium nitrite in water.
3. Solution of Potassium nitrite in water.
4. Tabloids (Burroughs Wellcome & Co's) of erythrol tetranitrate.
5. Chocolate tablets (Martindale's) of erythrol tetranitrate.
6. Chocolate tablets (Martindale's) of mannitol Hexanitrate.
7. Cobalto nitrite of Potassium in powder.
8. Liquor ethyl nitritis.

With the tabloids of nitroglycerine and of erythrol nitrate I was singularly unsuccessful in obtaining any depressor action. And in these cases I was forced to conclude that the nitroglycerine and the erythrol were either pharmacologically inert or that the tabloids remained unsolved. Even after hours of observation I obtained no action, a result never found if the nitroglycerine or erythrol were given in a form easily absorbed, - the former as liquor trinitrini and the latter in the form of chocolate/

systemic pressure and this method I employed in all my observations.

# NITRITES AND NITRATES EMPLOYED.

1. Tablets of Nitro glycerine and solution of ligustrin.

2. Solution of sodium nitrite in water.

3. Solution of potassium nitrite in water.



*Chart for blood pressure observations.*

the erythrol were either pharmacologically inert or that the tablets remained unabsorbed. Even after hours of observation I obtained no action, a result never found if the nitroglycerine or erythrol were given in a form easily absorbed. - the former as ligustrin and the latter in the form of

chocolate

chocolate tablets.

#### HOW TO RECORD PRESSURE.

The accompanying chart indicates the method I adopted for recording the changes in blood pressure following the use of nitrites.

The horizontal lines, as will be seen, indicate the height of blood pressure in millimetres of mercury rising in increments of 5 millimetres.

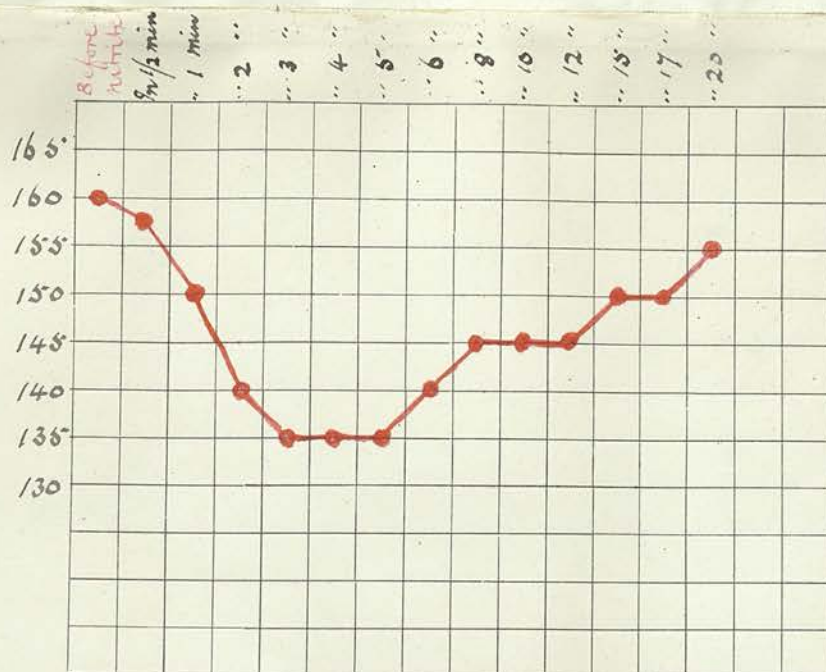
Along the top are figures indicating the **time** in minutes at varying intervals after the administration of the nitrite. The first space always indicates the pressure before the nitrite was given.

#### OBSERVATIONS WITH LIQUOR TRINITRINI.

As the tabloids of nitro-glycerine I employed gave negative results, the observations recorded were all made with the B. P. Solution of liquor trinitrini.

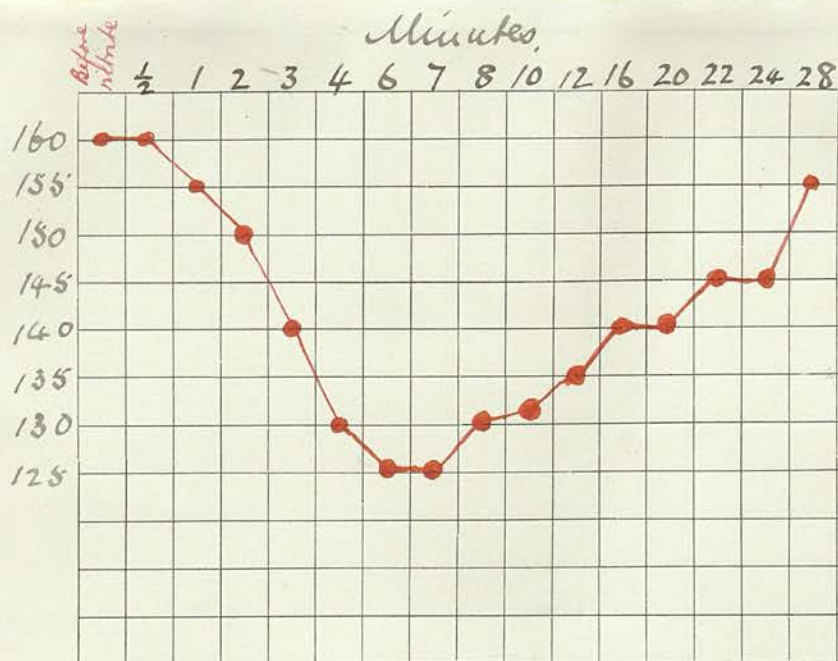
I made in all 12 observations in cases of hypertension and each is diagrammatically recorded on a separate chart on the following pages.

# Liquor Trinitrini observations.



2 minims Liquor Trinitrini

observation 1.



2 minims liquor trinitrini

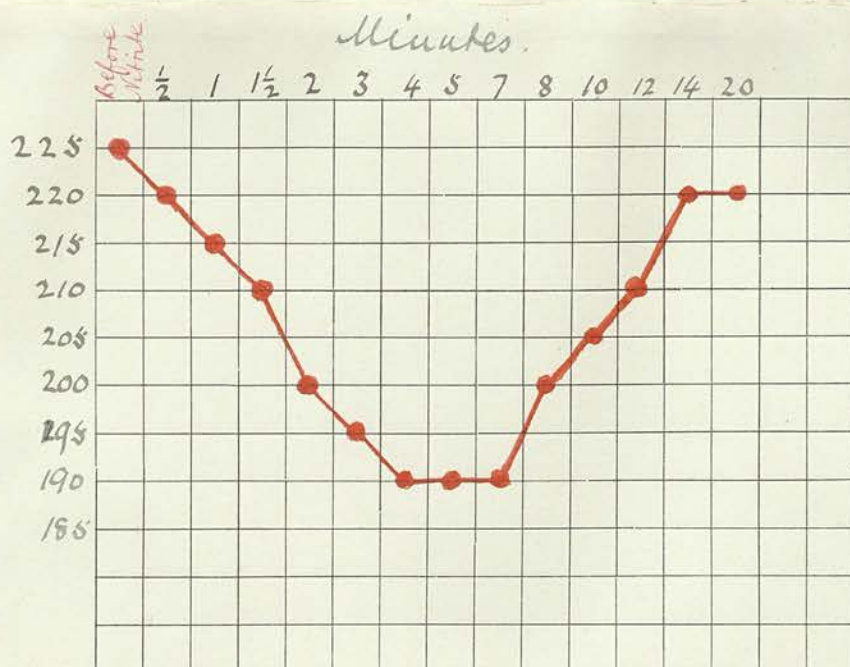
observation 2.





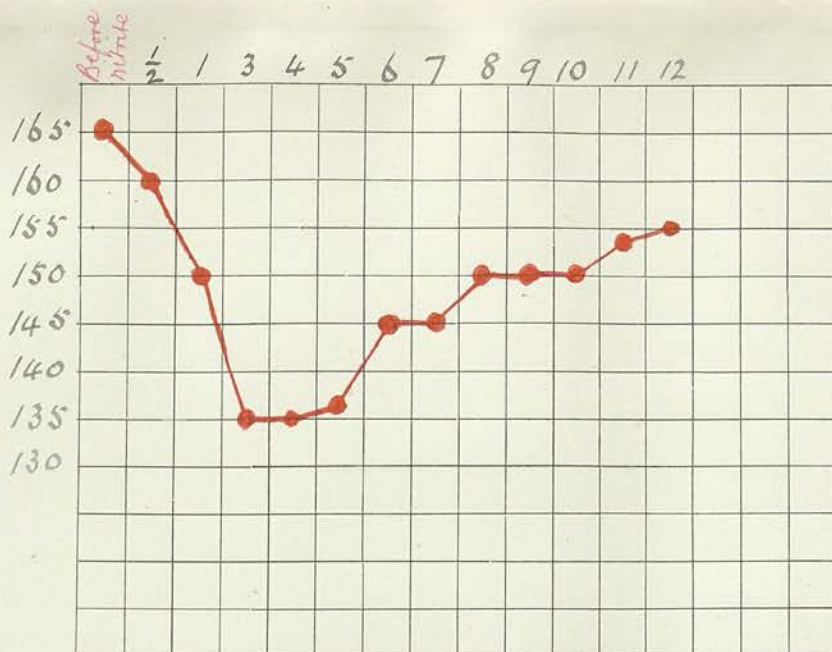
2 minims liquor trinitrini

observation 3



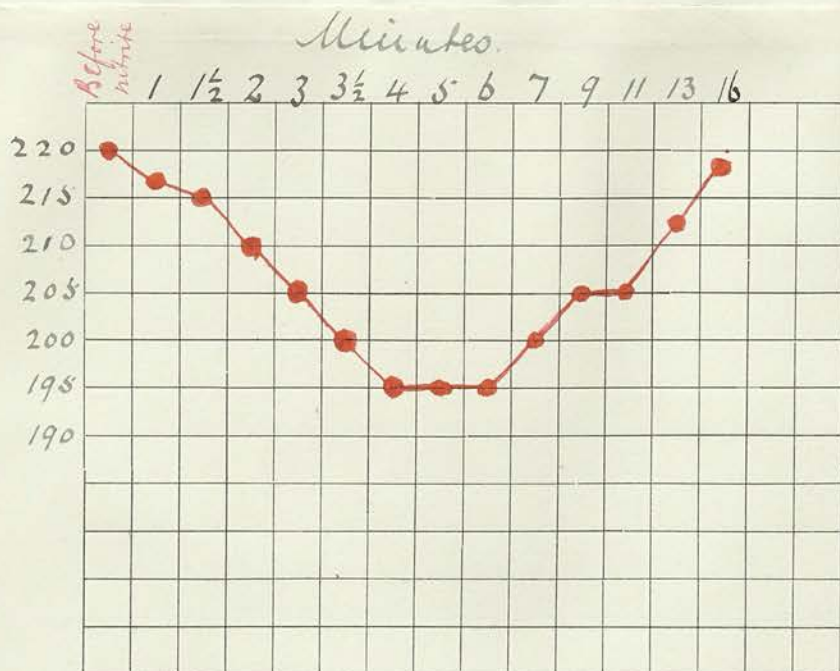
2 minims liquor trinitrini

observation 4



2 minus liquor trinitriui

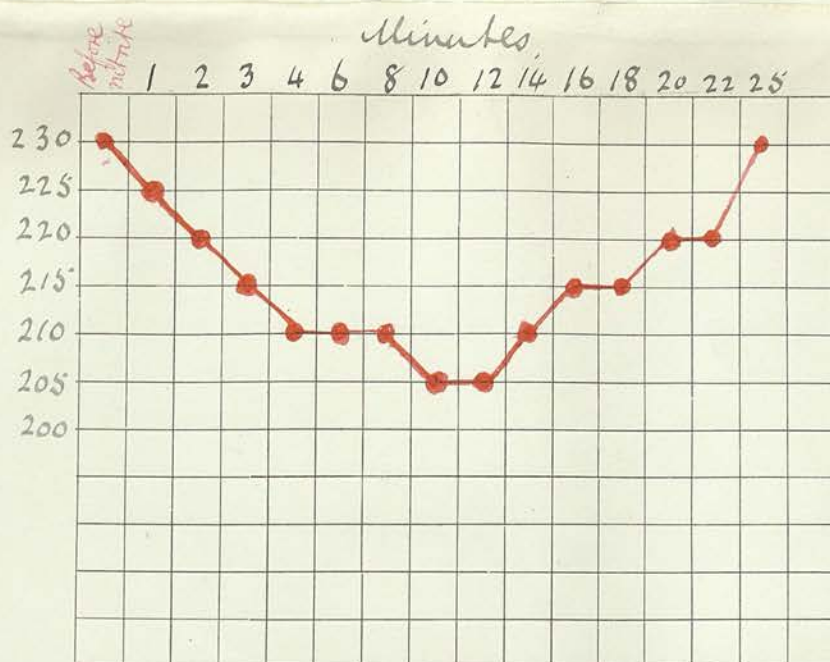
Observation 5.



2 minus liquor trinitriui

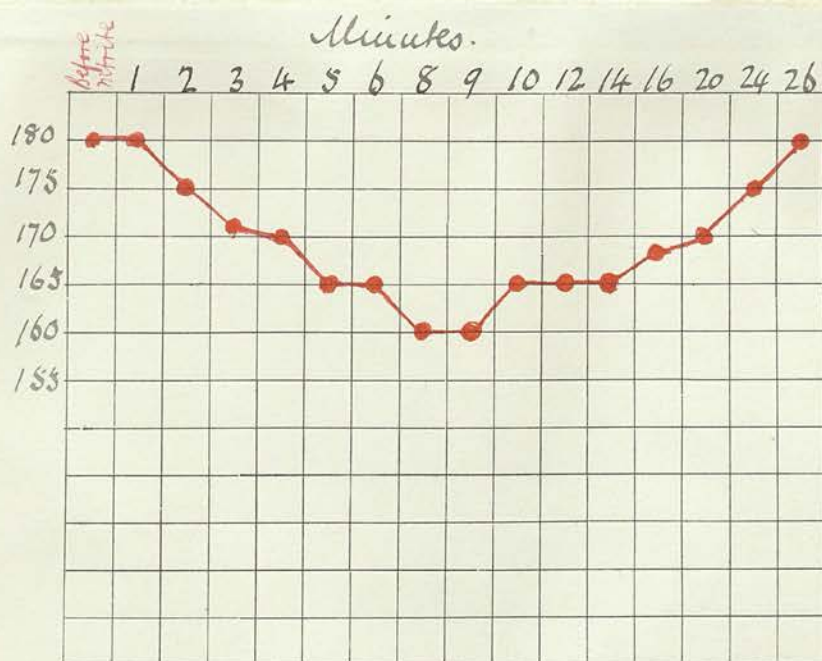
Observation 6





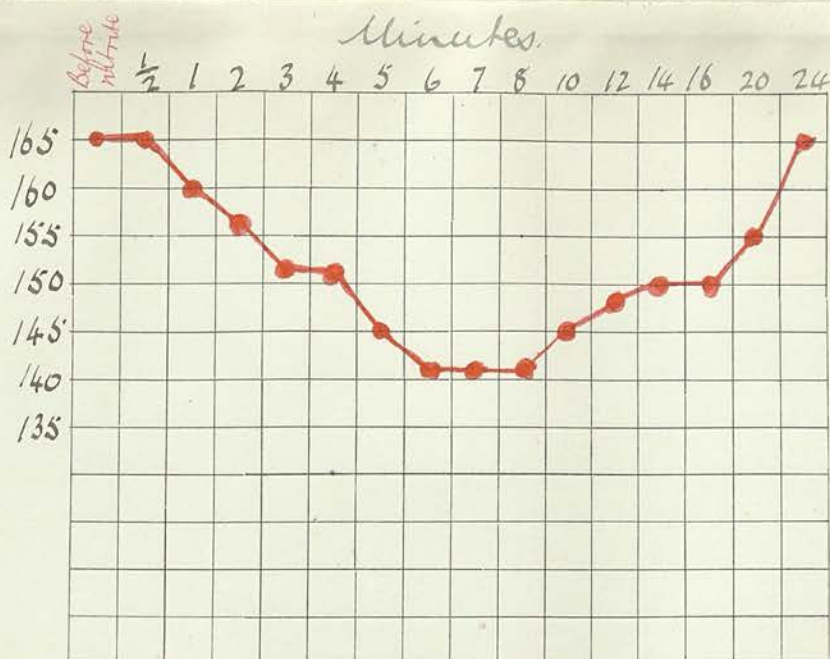
2 minus liquor trinitrini

observation 7



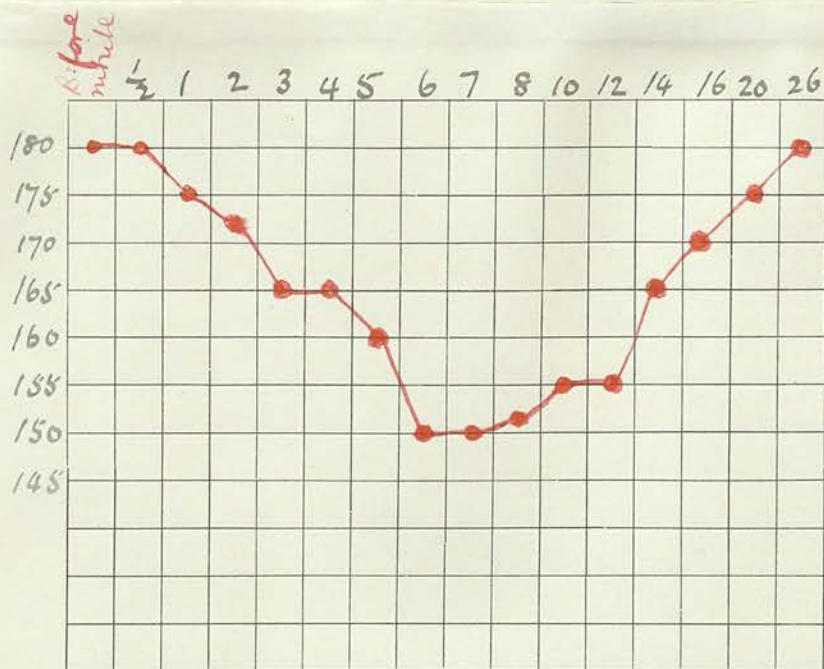
2 minus liquor trinitrini

observation 8



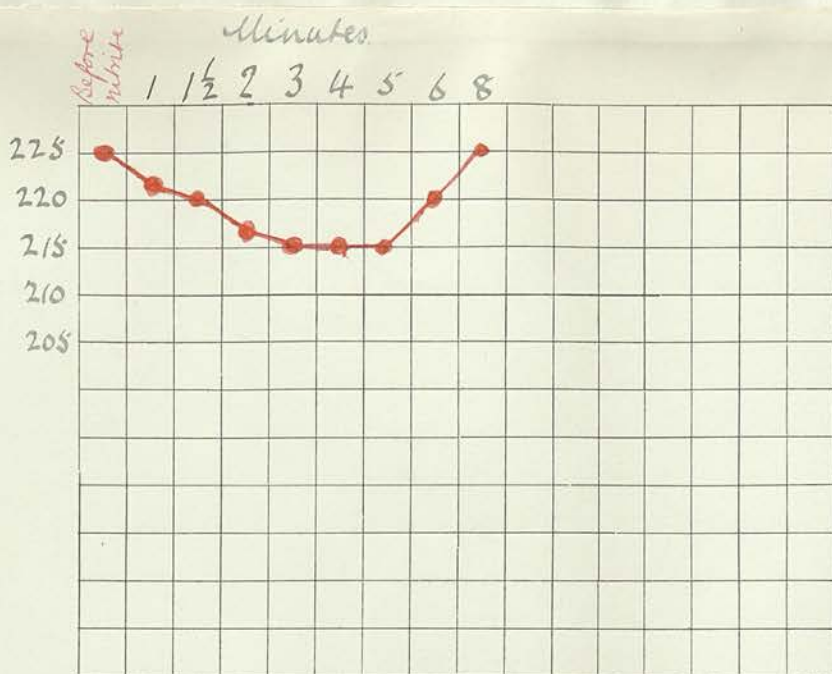
2 minims liquor trinitini

observation 9



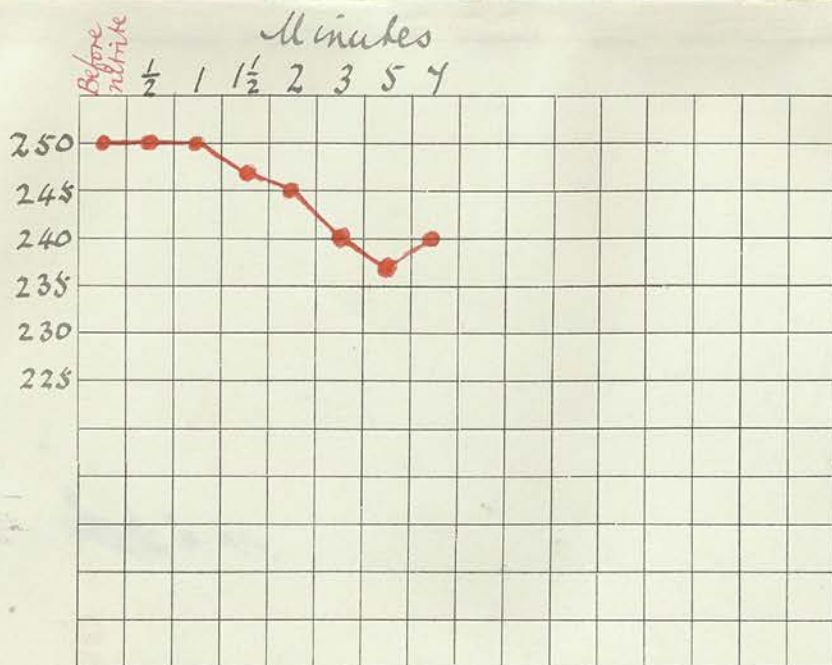
2 minims liquor trinitini

observation 10



2 minims liquor trinitrii

observation 11.



4 minims liquor trinitrii

observation 12.

From these charts it is possible to analyse the action of the drug *under* the headings I have already referred to.

1. Time in which the blood pressure begins to fall after the administration of liquor trinitrini.

Observation 1 in 30 seconds

"	2	"	60	"
"	3	"	30	"
"	4	"	30	"
"	5	"	30	"
"	6	"	60	"
"	7	"	60	"
"	8	"	90	"
"	9	"	60	"
"	10	"	60	"
"	11	"	60	"
"	12	"	90	"

From these figures it will be seen that the fall in pressure begins after a very short interval - varying from 30 to 90 seconds with an average of about a minute.

2. Amount of fall produced measured in millimetres of Mercury.

Observation/

OBSERVATION	1	25 millimetres	
"	2	35	"
"	3	30	"
"	4	35	"
"	5	30	"
"	6	25	"
"	7	25	"
"	8	20	"
"	9	25	"
"	10	30	"
"	11	10	"
"	12	12	"

I would draw particular attention to observations 11 and 12. There the fall was only 10 and 12 millimetres even though in the latter of the two a much larger dose was given. I would merely mention here that these two observations are examples of cases where the nitrite produces little or no action. They will be referred to later.

The average fall over the other 10 observations was 28 millimetres.



3. Time in which the maximum fall is attained.

Observation 1 in 3 minutes.

"	2	"	6	"
"	3	"	4	"
"	4	"	4	"
"	5	"	3	"
"	6	"	4	"
"	7	"	10	"
"	8	"	8	"
"	9	"	6	"
"	10	"	6	"
"	11	"	3	"
"	12	"	5	"

It will be observed that a maximum fall with liquor trinitrini in medicinal doses is produced with remarkable rapidity varying from 3 to 10 minutes. A glance at the charts, however, will indicate that the fall is not an absolutely abrupt one once the drug has begun to act, but gradual within the short time a maximum is developed.



4. Time during which the pressure remains at its lowest - or after which it again rises.

Observation 1 in 6 minutes.

"	2	"	7	"
"	3	"	11	"
"	4	"	8	"
"	5	"	6	"
"	6	"	7	"
"	8	"	14	"
"	7	"	10	"
"	9	"	10	"
"	10	"	8	"
"	11	"	6	"
"	12	"	7	"

The maximum effect, too, lasts only a very short time and in none of the observations was the maximum effect maintained for longer than 8 minutes.

5./

5. Time after which the pressure reaches its original level.

Observation	1	5 m.m. below original in 20 minutes		
"	2	in	28	minutes.
"	3	"	24	"
"	4	"	20	"
"	5	10 m.m. below original in 20 minutes.		
"	6	in	16	minutes
"	7	"	25	"
"	8	"	26	"
"	9	"	24	"
"	10	"	26	"
"	11	"	8	:
"	12	not observed.		

Number 5 is the most important result of all, indicating that in no case does the effect of a single dose of liquor trinitrini last more than 28 minutes. The rise towards the original level is slower, it will be seen, than the fall.

The action of a single medicinal dose of liquor trinitrini in hypertension may be summarised as follows:-

1./

1. Liquor trinitrini shows its vaso dilator action within one minute.
2. The amount of reduction is about 25 to 30 m.m.
3. The maximum effect is produced in a very short time viz. about 5 minutes.
4. The maximum reduction is maintained for only a few minutes and the original level is again reached within 28 minutes.

#### EFFECT OF REPEATED DOSES.

I made observations in suitable cases with liquor trinitrini given three or four times a day and in increasing doses as I wished to ascertain if by it one might be able to maintain a reduction in blood pressure.

I did not observe this in any case. But when one considers that the effect of a single dose has passed off in 28 or say 30 minutes a permanent reduction could only be expected by administration of the drug every half hour. But even then the desired effect is not attained. By giving the drug at short intervals and in increasing quantities I observed that a tolerance in most cases was established. Even when 30 and 40 minims had been given in the 12 hours, after the tolerance had been acquired/

acquired, I found the effect was only what one obtained from the original dose of 2 minims. No greater and no more lasting effect was produced by 10 minims than by two minims.

#### DOSAGE EMPLOYED IN THESE OBSERVATIONS.

My observations were made with two minim doses, except in one case where I gave increasing doses up to 8 minims for a particular purpose. In this case (observation 11) I had obtained little or no effect with the two minims and the increased amounts also had no greater effect.

I will refer later to the reason for using doses of two minims.

#### PECULIARITIES IN OBSERVATIONS 11 and 12.

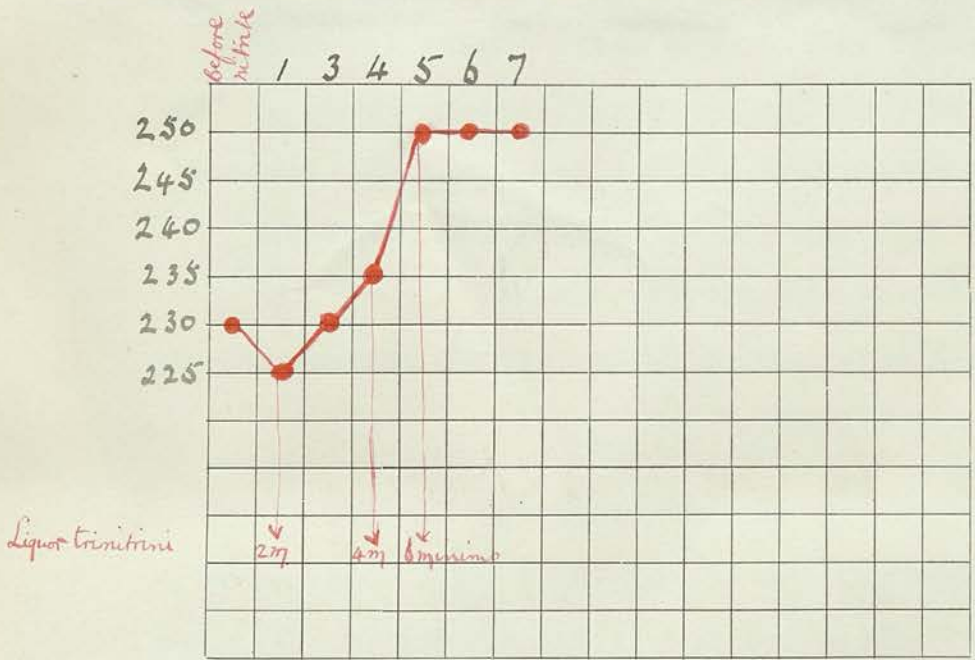
In observations 11 and 12, it will be observed, the liquor trinitrini had little effect on the blood pressure - the amount of reduction being 10 and 12 millimetres. The pressure in these two cases was high usually about 250 millimetres in observation 11 and 225 in No. 12. With the other nitrites - sodium and potassium, erythrol and mannitol I also failed in these two cases to obtain a vaso-dilator action.

I would merely mention here that there were cases of Cirrhotic Bright's Disease and that the condition/

acquired, I found the effect was only what was  
obtained from the original dose of 2 minims.  
No greater and no more lasting effect was produced  
by 10 minims than by two minims.

DOSEAGE EMPLOYED IN THESE OBSERVATIONS.

No observations were made with the minims



*Liqueur Trinitrinii for 6 days*

*advanced Cinchona bright*

millimetres. The pressure in these two cases was  
high usually about 850 millimetres in observation 11  
and 825 in No. 12. With the other minims - sodium  
and potassium, erythrol and mannitol I also failed  
in these two cases to obtain a vaso-dilator action.  
I would merely mention here that there were  
cases of Cinchona bright's disease and that the  
condition

condition when at all advanced is one where nitrites not only produce no action but may do harm.

#### HARM FOLLOWING ADMINISTRATION OF LIQUOR TRINITRIN.

In observation 11 after failure to secure a reduction of pressure by a single dose I wished to ascertain if any effect could be produced by continuous administration over a period of days.

For this purpose I put the patient on 2 minims t.i.d. to start with. This was gradually increased and on the 5th day he was having 8 minims t.i.d. The nitrite was stopped on the 7th day and the accompanying chart shows the effect on the blood pressure.

At the end of first day the pressure had evidently dropped a very little = 5 millimetres. With the increase of the nitrite the pressure instead of falling gradually rose, and on the 7th day was 250 m.m. of mercury. Concomitantly the patient began to have unpleasant symptoms. On the 5th day he complained of violent headache, chiefly occipital and pulsating in character. On the 6th day he became short of breath and was unable to lie down and he became sleepless. In the meantime no change was observed in the amount of urine passed or in the amount of albumen which had always been small.

On/



On the 8th day dulness appeared on the left side of the thorax and 32 ounces of deeply blood stained fluid was drawn off, followed on the 10th day by 40 ounces of similar fluid from the right side of the chest. After the nitrite was stopped and the fluid had been drawn off the headaches and other symptoms gradually subsided.

Subsequently in similar cases of Cirrhotic Bright's Diseases I observed the same tendency with continued and increasing doses of liquor trinitrini. Headache set in after a few days followed by shortness of breath. In these I always stopped the nitrite, on the appearance of headache, with beneficial results.

OBSERVATIONS WITH SODIUM NITRITE AND POTASSIUM  
NITRITE.

These were made with freshly prepared solutions of these drugs, which were administered under the same conditions as liquor trinitrini.

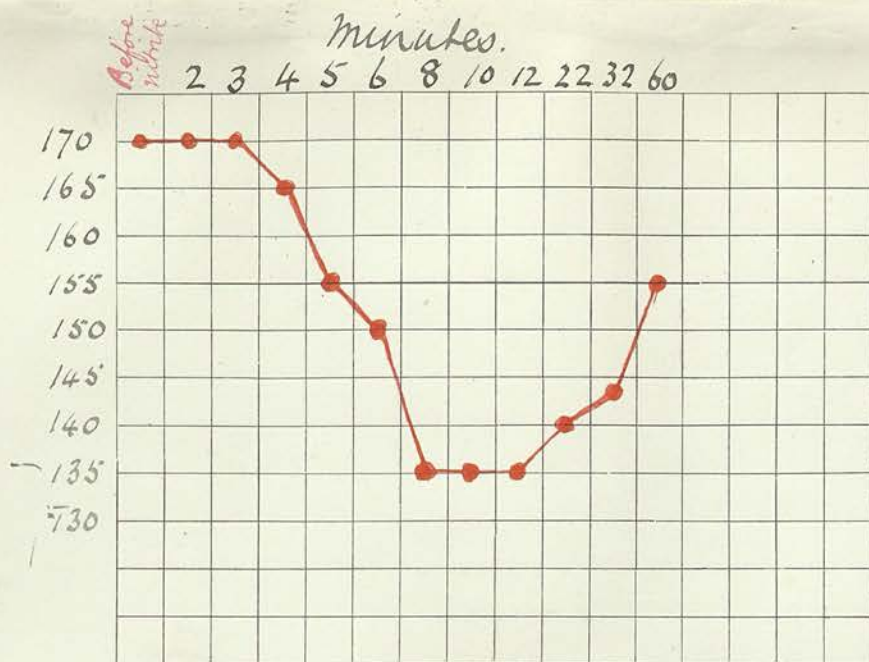
Some of the observations were made in the same cases as liquor trinitrini in order to obtain a comparison between the various nitrites - others in different hypertension cases.

As might have been expected I could detect no difference in their action between sodium and potassium ~~nitrites~~ - both acted equally well.

Twenty observations were made in all. They are represented on the accompanying charts. The analysis will be followed under the same headings as liquor trinitrini.

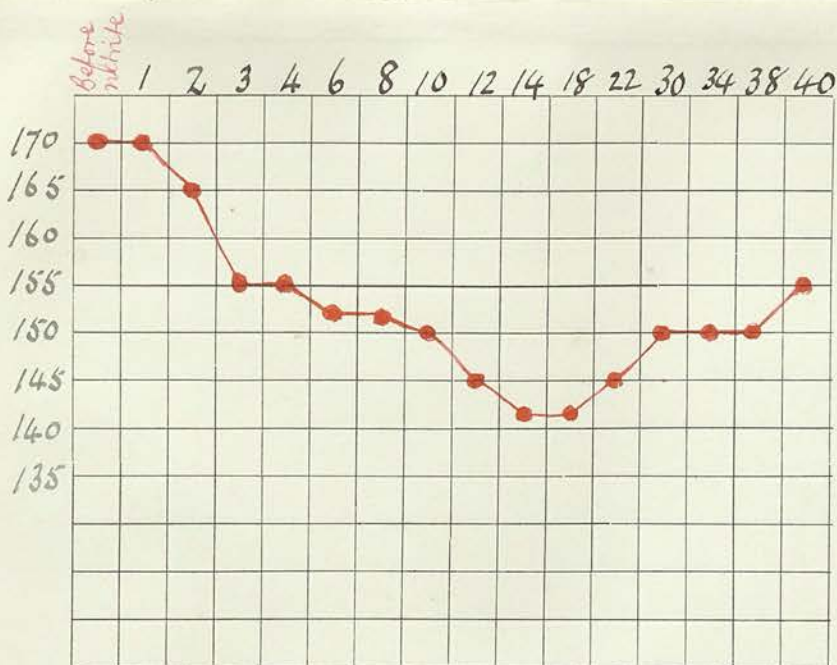
1./

# Sodium and Potassium nitrite observations.



3 grains Potassium nitrite

observation 1



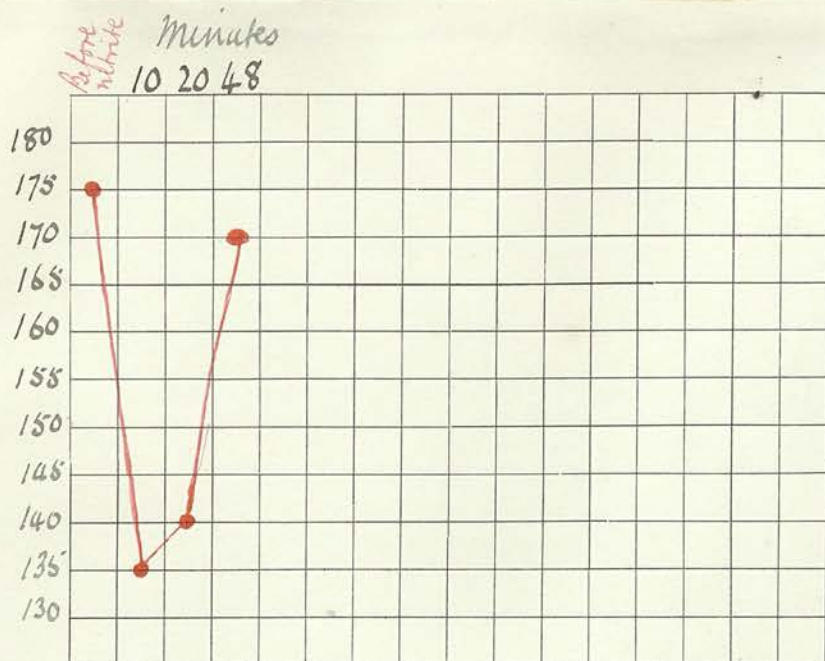
2 grains Potassium nitrite

observation 2



2 grains sodium nitrite

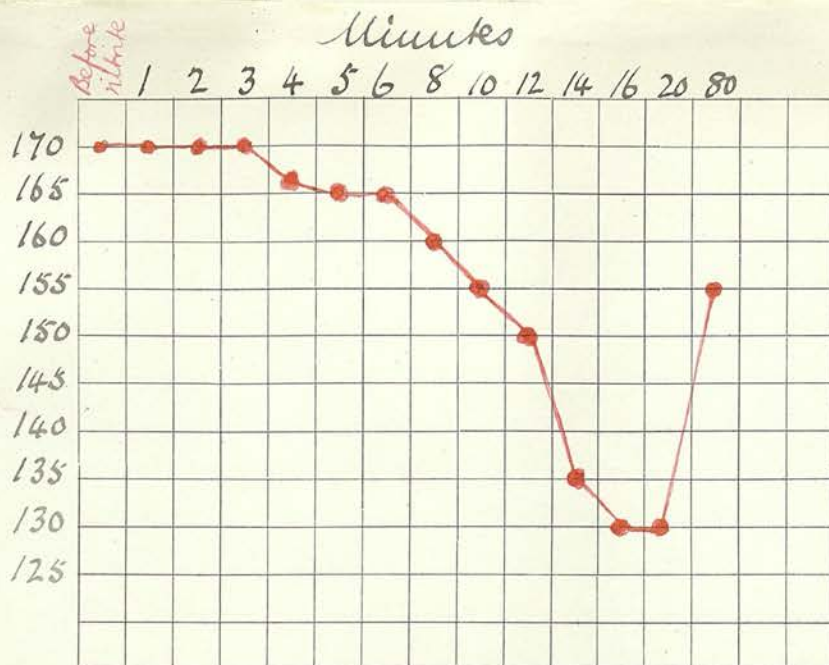
observation 3.



2 grains sodium nitrite

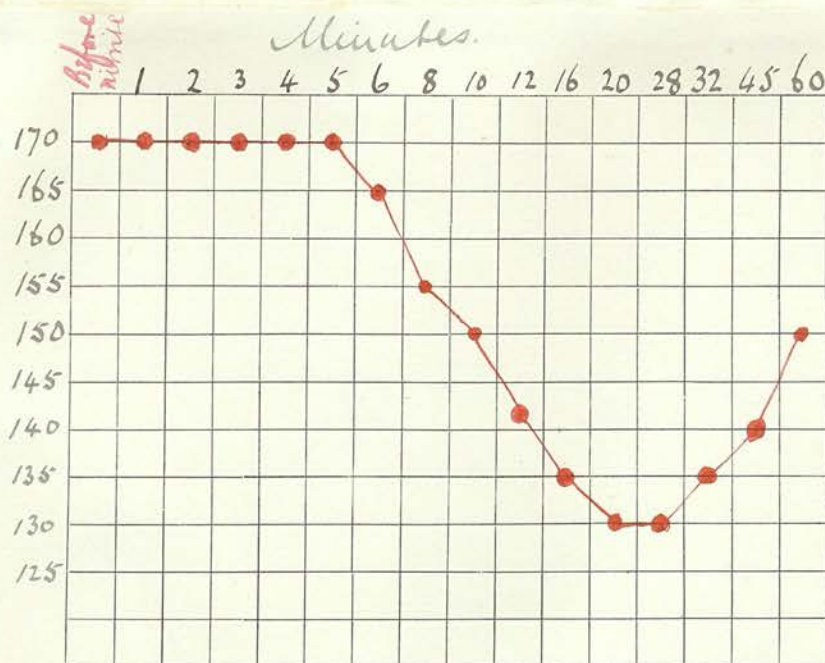
observation 4.





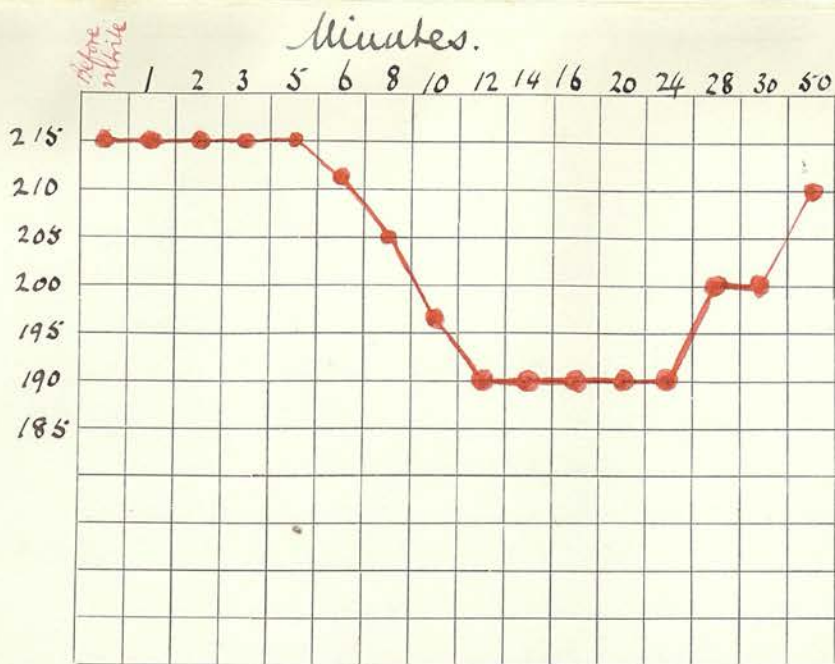
2 grains sodium nitrite

observation 5



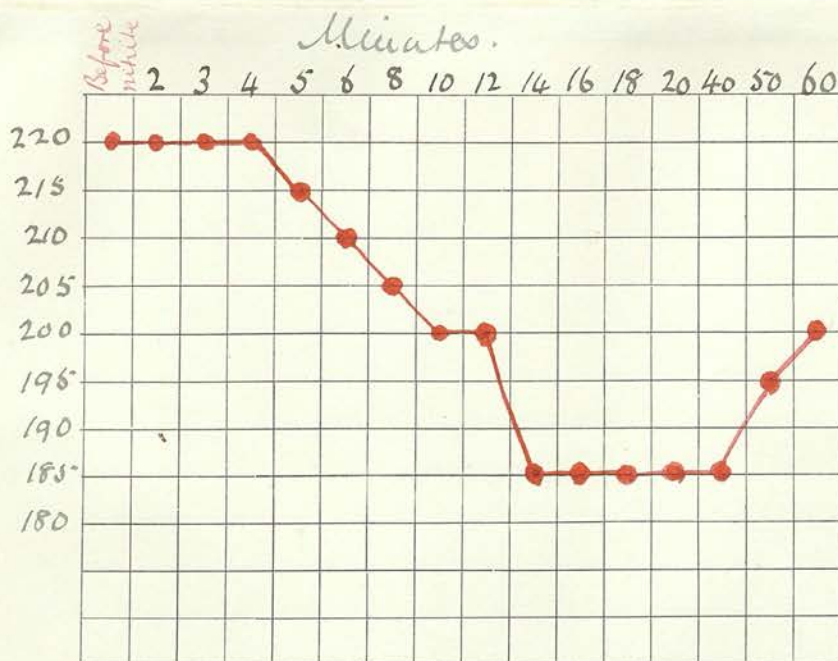
3 grains potassium nitrite

observation 6



3 grains Potassium nitrite

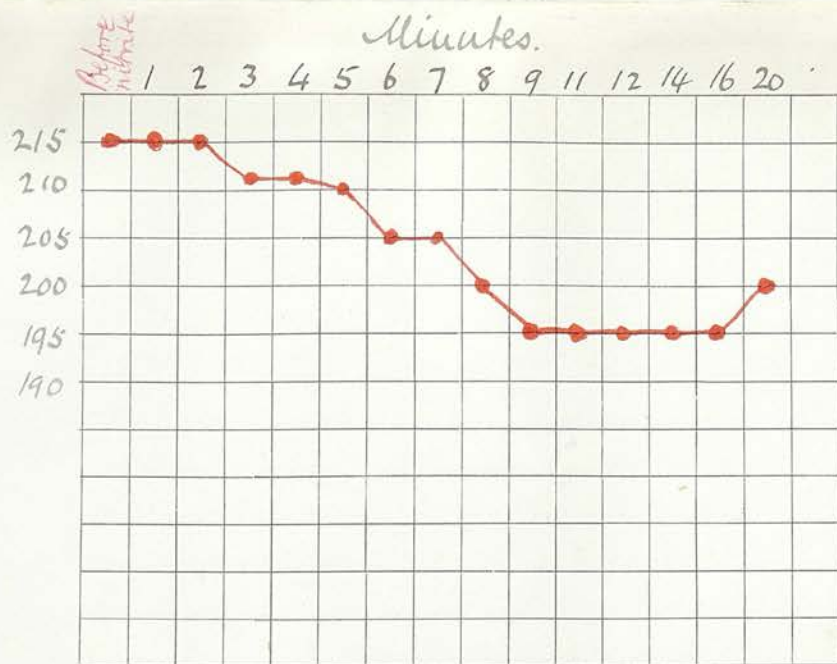
Observation 7



3 grains Potassium nitrite

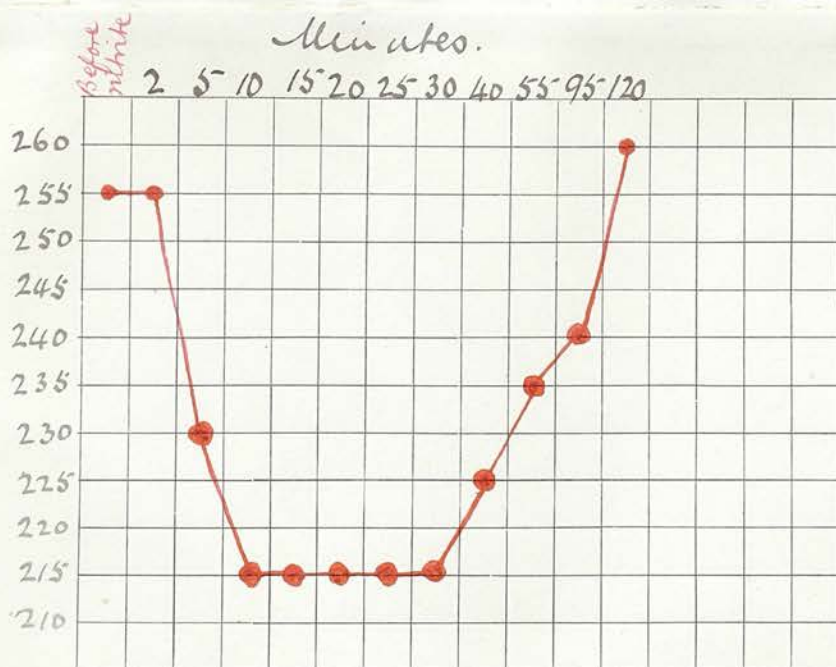
Observation 8.





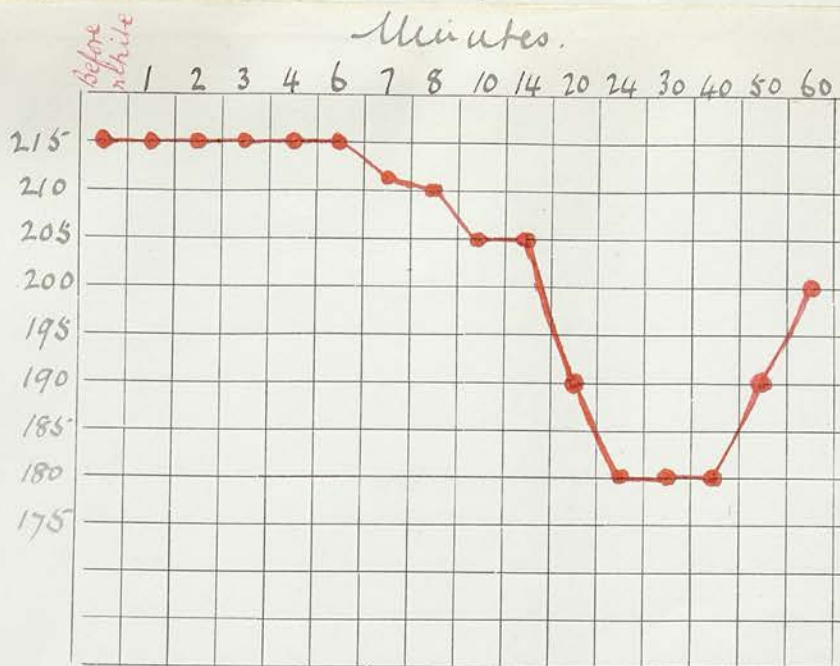
2 grains Potassium nitrite

observation 9



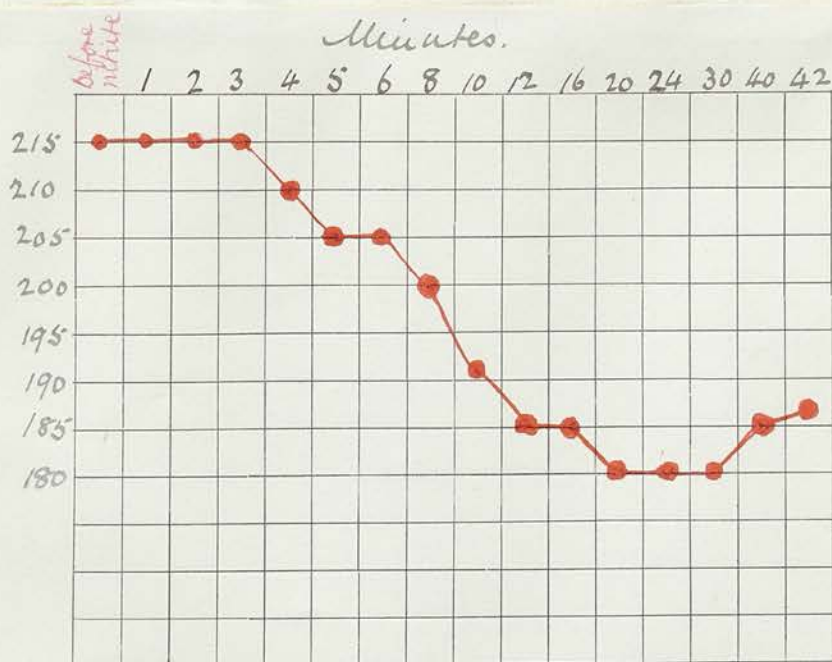
2 grains Sodium nitrite

observation 10



3 grains Sodium nitrite

Observation 11



3 grains Potassium nitrite

Observation 12



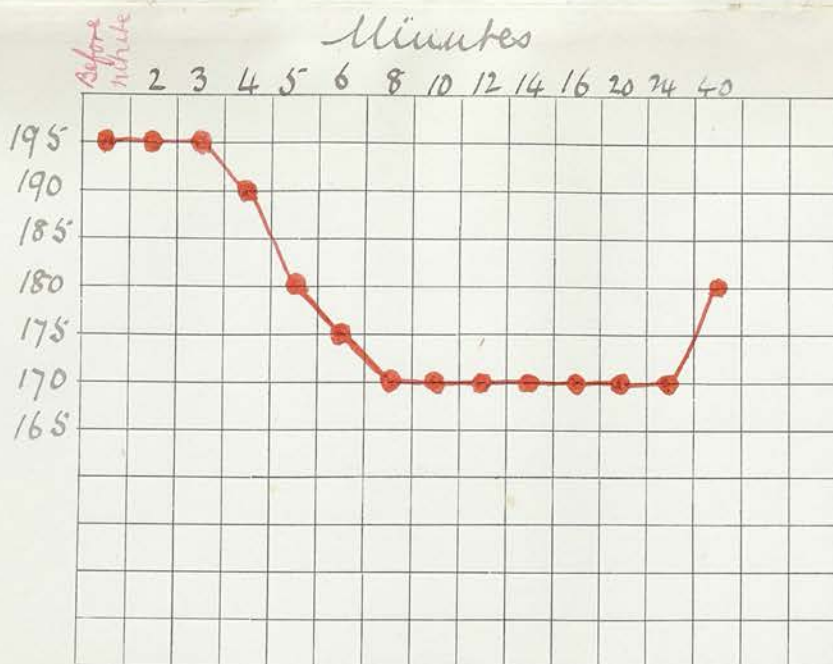
2 grains sodium nitrite

Observation 13



3 grains Potassium nitrite

Observation 14



2 grains Sodium nitrite

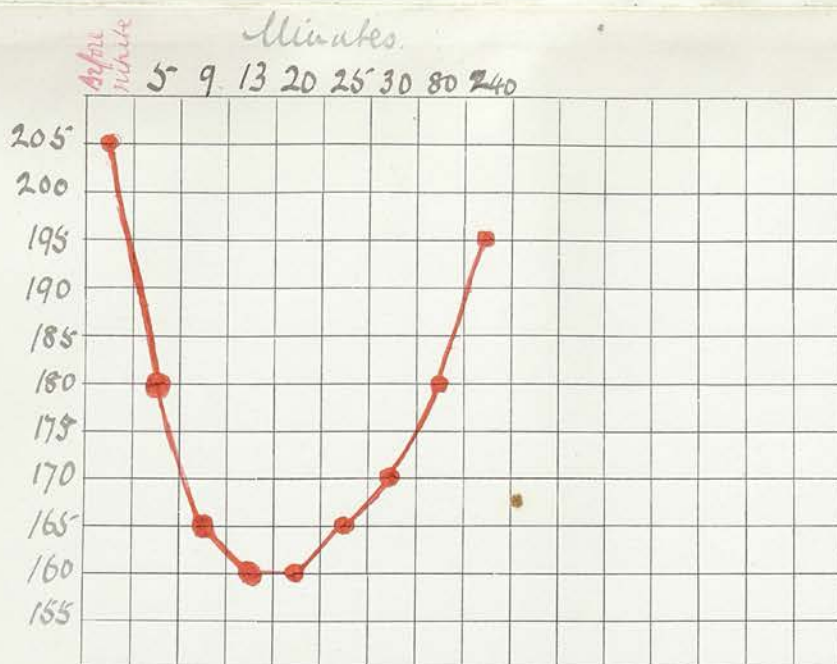
observation 15



2 grains Potassium nitrite

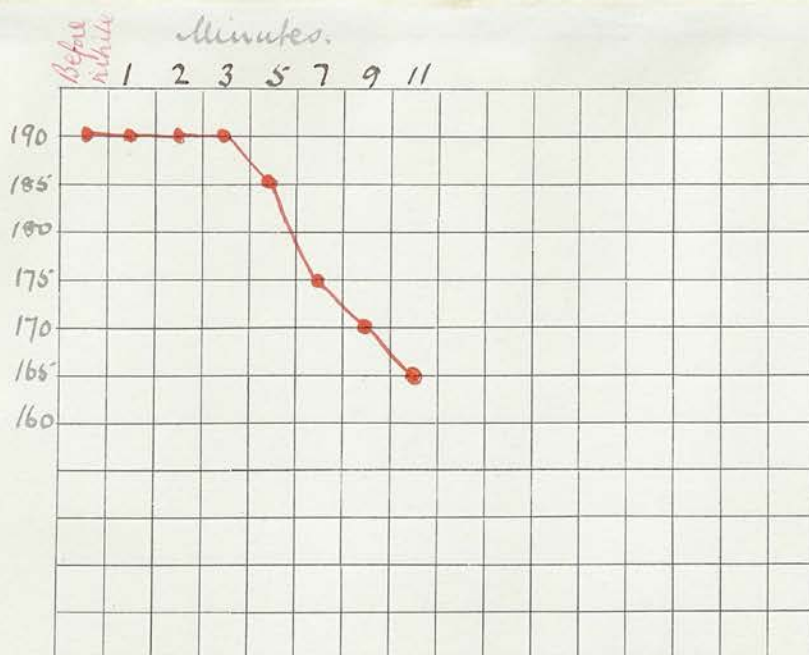
observation 16





2 grains sodium nitrite

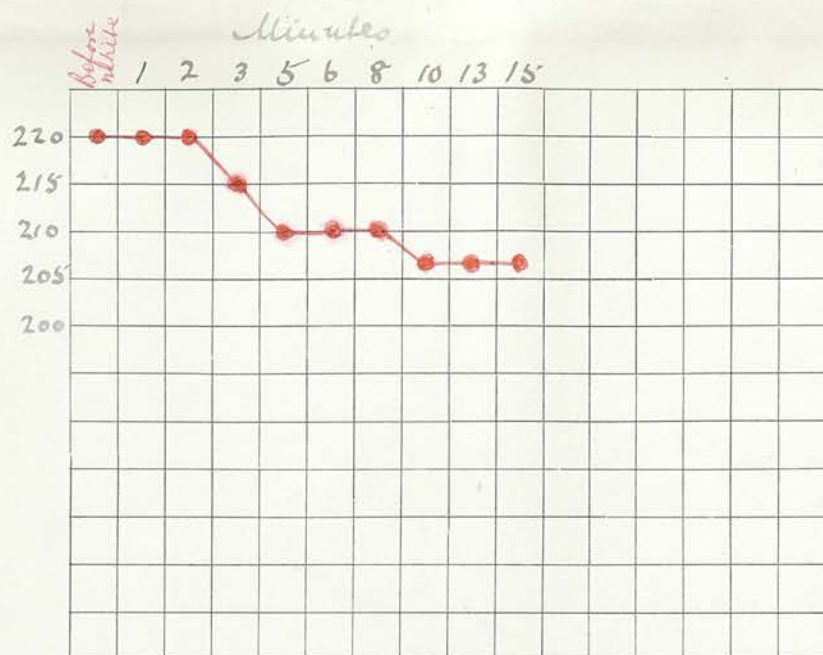
Observation 17.



observation  
for 11 minutes  
only.

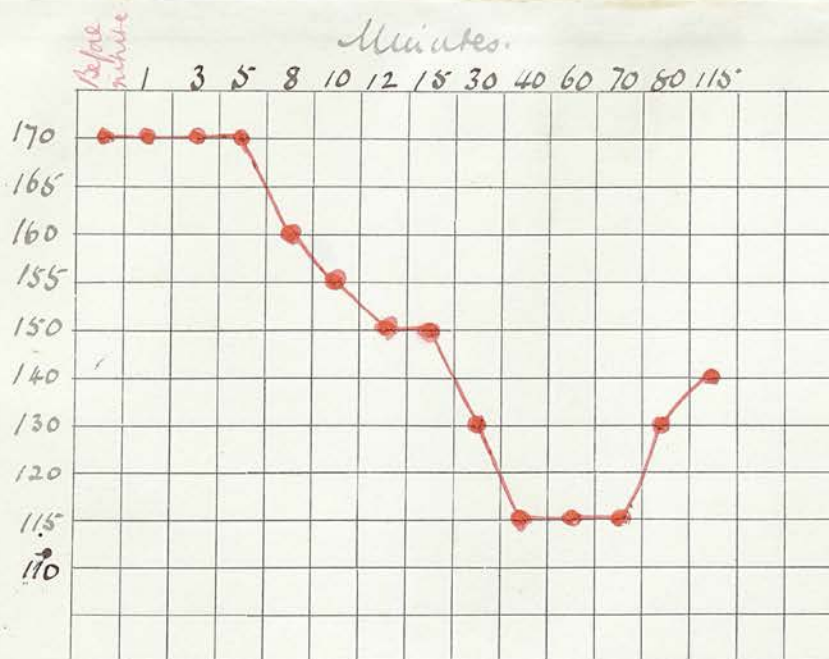
2 grains sodium nitrite

Observation 18



2 grains sodium nitrite

Observation 19



2 grains sodium nitrite

Observation 20.



1. Time in which the pressure begins to fall  
after the administration of the nitrite.

OBSERVATION	1	in	4	minutes.
"	2	"	2	"
"	3	"	3	"
"	4		not observed.	
"	5	"	4	minutes.
"	6	"	6	"
"	7	"	6	"
"	8	"	5	"
"	9	"	3	"
"	10	"	not observed.	
"	11	in	7	minutes.
"	12	"	4	"
"	13	"	6	"
"	14	"	3	"
"	15	"	4	"
"	16	"	4	"
"	17		not observed	
"	18	"	4	minutes
"	19	"	3	"
"	20	"	6	"

Sod. and Pot. nitrite do not act with the promptness of liquor trinitrini. In these 20 observations the time varied from two minutes to seven minutes with an average of these observed of almost exactly 4 minutes.

2. Amount of fall measured in millimetres of mercury.

Observation	1	35 m.m. of Hg.			
"	2	30	"	"	"
"	3	35	"	"	"
"	4	40	"	"	"
"	5	40	"	"	"
"	6	50	"	"	"
"	7	25	"	"	"
"	8	35	"	"	"
"	9	20	"	"	"
"	10	40	"	"	"
"	11	35	"	"	"
"	12	35	"	"	"
"	13	30	"	"	"
"	14	30	"	"	"
"	15	25	"	"	"
"	16	20	"	"	"
"	17	45	"	"	"
"	18	25	"	"	"
"	19	12	"	"	"
"	20	55	"	"	"

In observation 19 very little fall was got. I have excluded from the table other cases where I found the same result and included it only as an example of a condition where the nitrite did not act. Over the other 19 observations the average fall is 32.5 millimetres of mercury.

This amount is about 20 per cent greater than with liquor trinitrini and about represents the figure I obtained when the two drugs were tried in the same case.

3. Time in which the maximum fall is reached.

Observation 1 in 8 minutes.

"	2	" 14	"
"	3	" 13	"
"	4	" 10	"
"	5	" 16	"
"	6	" 20	"
"	7	" 12	"
"	8	" 14	"
"	9	" 9	"
"	10	" 10	"
"	11	" 24	"
"	12	" 20	"
"	13	" 20	"
"	14	" 18	"
"	15	" 8	"
"	16	" 8	"
"	17	" 13	"
"	18	not observed	
"	19	" 15 minutes	
"	20	" 40	"

After a single dose of the nitrite the lowest point is reached in a comparatively short time varying over 18 observations (excluding 18 and 19) from 8 to 40 minutes (the latter only in one case) with an average of 15.4 minutes. As will be seen from the charts the fall is a gradual one during the 15 minutes, amounting to about 5 m.m. of Hg. every 2 minutes until the full effect is produced.

4. Time after which the pressure again begins to rise.

Observation	1	in	22	minutes.
"	2	"	22	"
"	3		between 28 & 40	minutes
"	4		not observed.	
"	5		after 20	minutes.
"	6		in 32	minutes.
"	7	"	28	"
"	8		between 40 & 50	minutes.
"	9	"	20	minutes
"	10		between 30 & 40	minutes
"	11		" 40 & 50	"
"	12		" 30 & 40	"
"	13		" 30 & 50	"
"	14		" 50 & 70	"
"	15		" 24 & 40	"
"	16	"	24	minutes.
"	17	"	25	"
"	18		not observed	
"	19		not observed	
"	20		between 70 & 80	minutes.

The maximum effect with sodium and potassium nitrite is maintained for a varying period the shortest being 20 minutes and the longest between 70 and 80 minutes calculating from the time the nitrite was administered.

5. Time in which the pressure reached its original level.

It was not possible in all cases to ascertain this probably the most important of all, as time and the exigencies of the Ward did not permit.

Sufficient however was observed for the purpose of ascertaining the approximate total duration of a single dose of Sodium or of Potassium nitrite.

Observation	1.	after 60 minutes,	pressure still 15 m.m. below original level								
"	2.	"	40	"	"	"	15	"	"	"	"
"	3.	"	48	"	"	"	15	"	"	"	"
"	4.	"	48	"	"	had reached original level.					
"	5.	"	80	"	"	still 20 m.m. below original level					
"	6.	"	60	"	"	"	20	"	"	"	"
"	7.	"	50	"	"	"	5	"	"	"	"
"	8.	"	60	"	"	"	20	"	"	"	"
"	9.										
"	10.	"	120	"	"	had risen 5 m.m. above original					
"	11.	"	60	"	"	still 15 m.m. below original level					
"	12.	"	42	"	"	"	30	"	"	"	"
"	13.	"	80	"	"	"	15	"	"	"	"
"	14.	"	105	"	"	"	15	"	"	"	"
"	15.	"	40	"	"	"	15	"	"	"	"
"	16.	"	40	"	"	"	10	"	"	"	"
"	17.	"	240	"	"	"	10	"	"	"	"
"	18.	not observed									
"	19.	not observed									
"	20.	after 115 minutes		"	"	"	30	"	"	"	"

From these figures it will be seen that the action of sodium and Potassium nitrites is maintained over a considerable period. In none of the observations had the pressure returned to its normal in one hour and in a considerable number of them the pressure is still down after 2 hours and more.

The rise after the maximum effect begins to pass off is only a very gradual one and one may say that these drugs still remain active over a period varying from an hour to over two hours.

#### SUMMARY.

Summarising these observations with sodium and potassium nitrite in a single therapeutic dose we may conclude.

1. Their vaso dilator action is produced in five minutes.
2. The amount of reduction of the blood pressure is 32.5 m.m. of Hg.
3. The maximum effect is produced in 15 minutes.
4. Though the maximum fall is seen in 15 minutes the return of the pressure towards its normal is very gradual, the effect lasting well over an hour and in a number of the cases over two hours.

EFFECT/



EFFECT OF REPEATED AND CONTINUED DOSES.

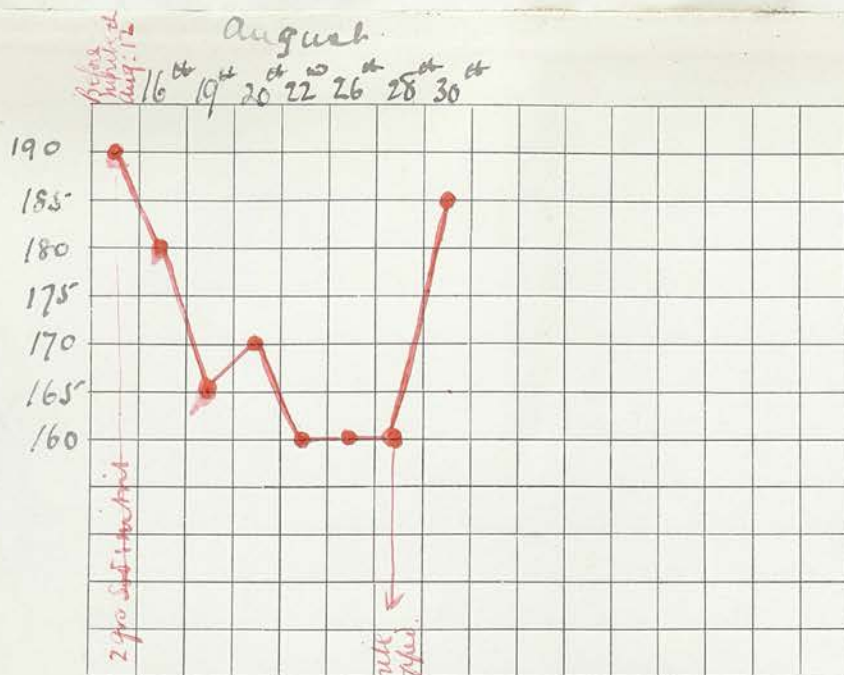
As I have just shown a single dose of sodium nitrite remains active for about two hours, <sup>and</sup> it might therefore be expected that a course of the nitrite might assist in maintaining a reduction of pressure during the exhibition of the drug.

Several of the cases that I found responded well to a single dose were given sodium or potassium nitrite three or four times a day in doses of two or three grains. The pressure was then estimated every day, and two or three times a day, care being taken not to estimate too soon after any of the doses. With them I did not observe the same tendency to tolerance as with liquor trinitrini nor did I find any unpleasant effects from their use in medicinal doses.

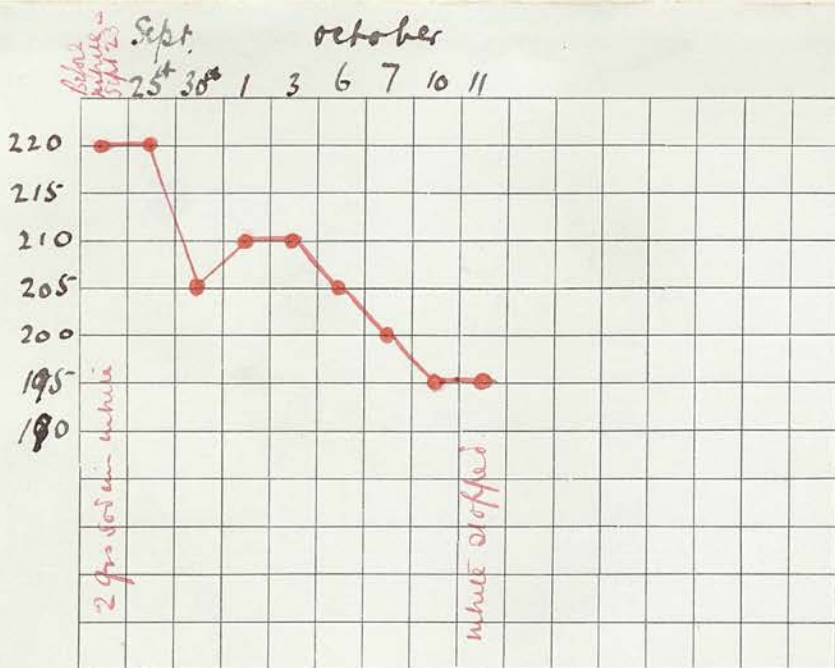
The two following charts shew the effects in suitable cases.

In observation 1 the patient ~~was~~ put on 2 grains sodium nitrite t.i.d. on 12 th August. This was stopped on 28th August. During that time the pressure was maintained as a level about 25 to 30 m.m. lower than it had originally been. After the nitrite was stopped on the 28th August the pressure promptly rose again to its original amount on the 30th. The pressure remains down only during the administration.

In/



2 grains Sod in milk three times a day.



2 grains Sod in milk three times a day.

In observation 2 the patient was put on 2 grains sodium nitrite on September 23rd. By September 30th the pressure had fallen from 220 m.m. to 205 m.m. and by October 11th it was 195 m.m. On this day the patient left hospital and no further observations could be made.

In suitable cases therefore - and these will be found by observing the action of a single dose - sodium and potassium nitrites help in maintaining a reduction of pressure below an original high level. The amount of reduction is about similar to what is got with a single dose. The effect passes off very quickly after the nitrite is stopped.

I made observations also with continued doses in cases of which 19 of the series is an example. In this case a single dose had little or no action and I found the same with the nitrite given three times a day over a period.

Carter of New York in 1901 made a few observations with sodium nitrite in hypertension. He made 10 observations with sodium nitrite in doses varying from  $\frac{1}{2}$  to three grains. Five observations were with a single dose.

He found in these five cases the vaso dilator action produced in from 10 to 50 minutes with an average of 26 minutes. The amount of reduction was/

was from 10 to 15 millimetres of mercury and the effect lasted from 1 to 2 hours - average 1 hour 40 minutes.

One result was negative - a chronic nephritis with acute exacerbation and uraemia.

His observations were made with the sphygmometer - the indicator of which was a metal tambour

Its expansion was exhibited in a highly magnified form by means of an index or pointer travelling round a dial.

My investigations with the more modern blood pressure instruments do not agree with Carters. In a single dose (in cases which respond) I have always found sodium nitrite act much more quickly than 26 minutes, and in none of my observations ~~was~~ the action delayed for 50 minutes. I also obtained a much greater fall in pressure. I agree with him that a single dose of sodium nitrite has an effect lasting for about two hours.

He found in his other five observations that its continued use has a greater and more lasting effect than a single dose, the beneficial effect lasting while the drug is continued. This agrees with my observations.

DOSAGE/

DOSAGE EMPLOYED.

My observations were made entirely with doses of two and three grains. Previously I had made several with small doses of  $\frac{1}{2}$  grain, but the effect was slight and I adopted two and three grain doses for reasons I will afterwards detail. I was not able to discriminate between the two and three grain doses, both producing about the same effect in the same patient.

OBSERVATIONS WITH ERYTHROL TETRANITRATE.

I made first of all seven observations with fresh Burroughs, Wellcome & Co's tabloids in doses of  $\frac{1}{2}$  and 1 gr.

Observation 1.	Dose 1 gr.	No change in pressure in $3\frac{1}{2}$ hours.						
" 2.	" 1 gr.	"	"	"	"	"	"	25 minutes.
" 3.	" 1 gr.	"	"	"	"	"	"	1 hour 40 minutes.
" 4.	" 1 gr.	"	"	"	"	"	"	1 hour 10 minutes.
" 5.	" $\frac{1}{2}$ gr.	"	"	"	"	"	"	36 minutes.
" 6.	" $\frac{1}{2}$ gr.	"	"	"	"	"	"	1 hour 25 minutes.
" 7.	" $\frac{1}{2}$ gr.	"	"	"	"	"	"	1 hour 40 minutes.

These observations were made in the same patients in whom subsequently I obtained a positive result with another preparation of the drug./

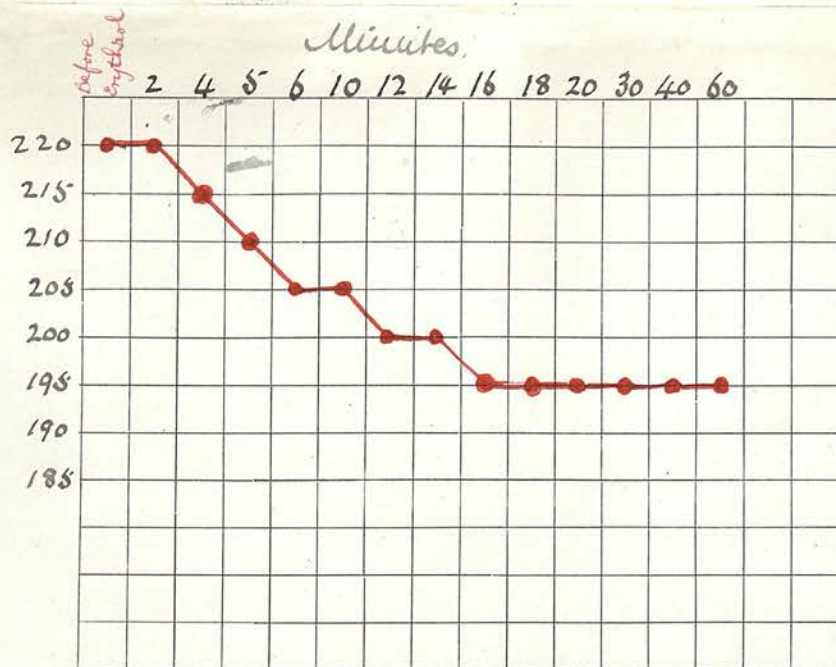


drug. Having failed with these tabloids I employed Martindale's chocolate tablets. They have a chocolate basis and dissolve readily by suck<sup>ing</sup> in the mouth.

OBSERVATION WITH MARTINDALE'S CHOCOLATE  
TABLETS OF ERYTHROL.

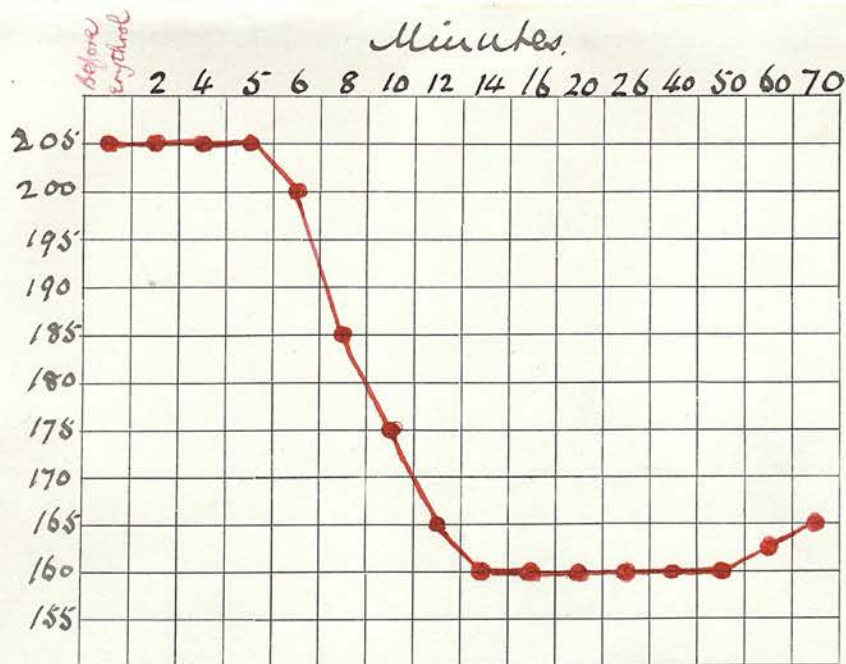
I made 14 observations in all. The accompanying charts readily show the action of the drug and the analysis brings out the requisite points. (see next page)

# Erythrol Tetranitrate observations.



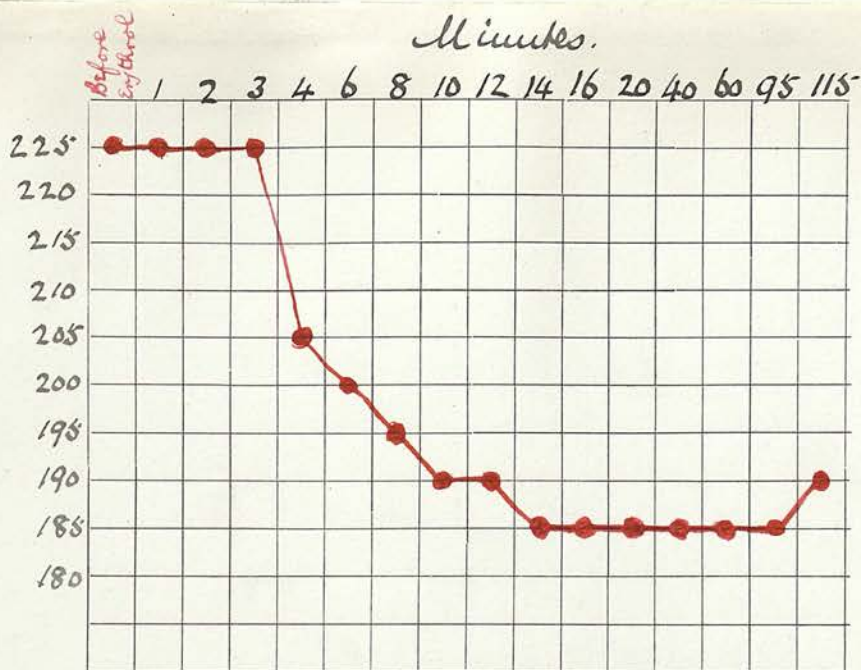
1/2 Grain Erythrol tetranitrate

observation 1



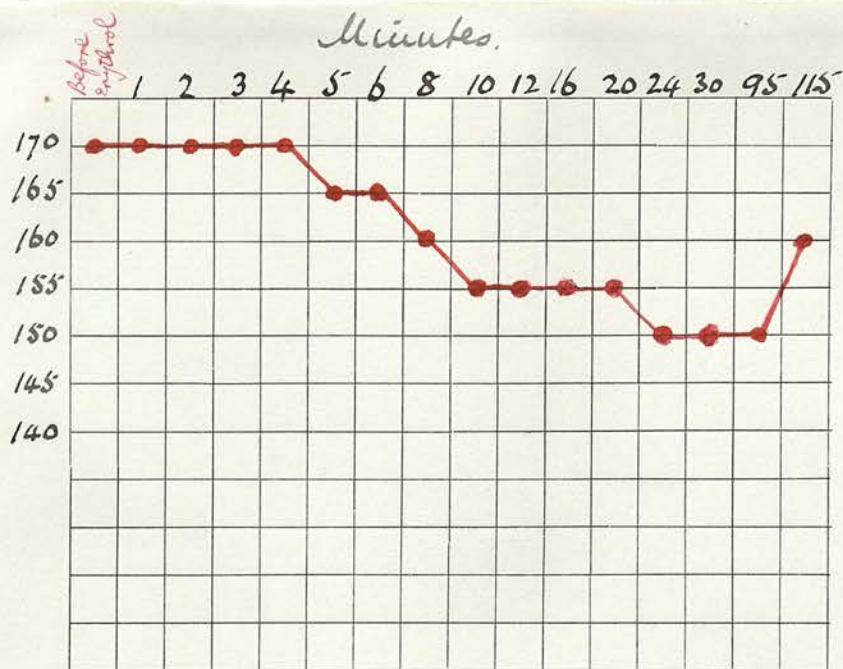
1 Grain Erythrol nitrate

observation 2



1 Grain Erythrol nitrate

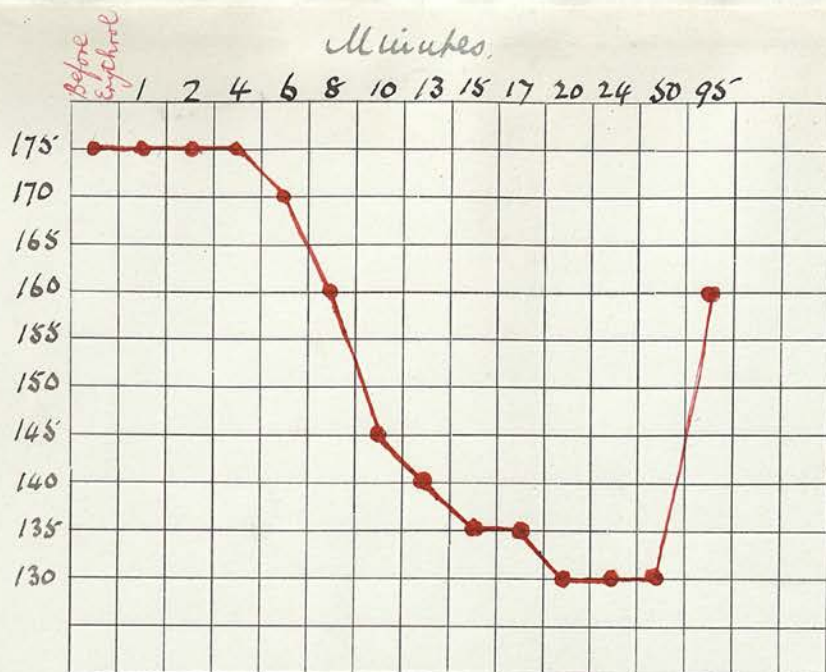
observation 3



1 Grain Erythrol nitrate

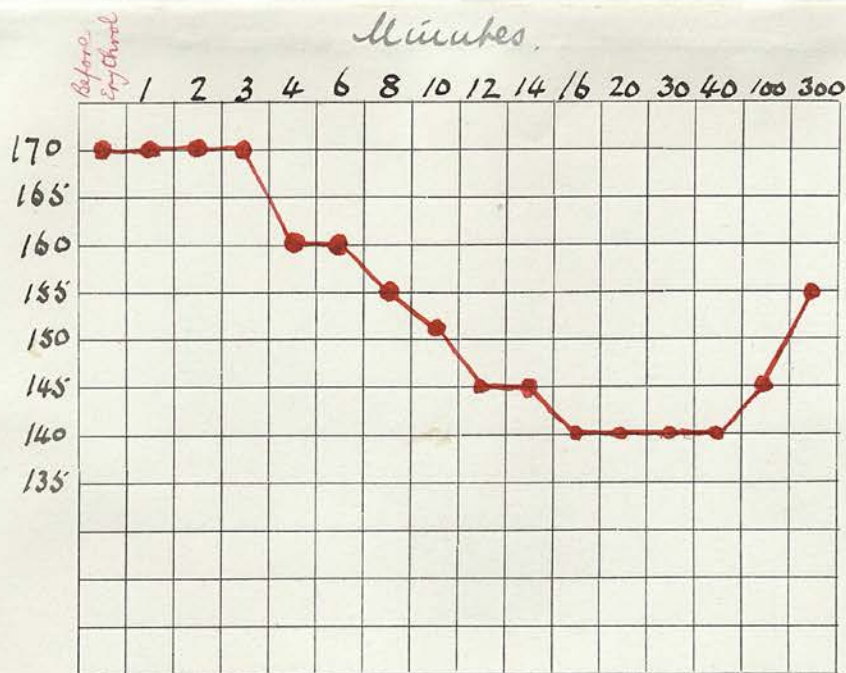
observation 4





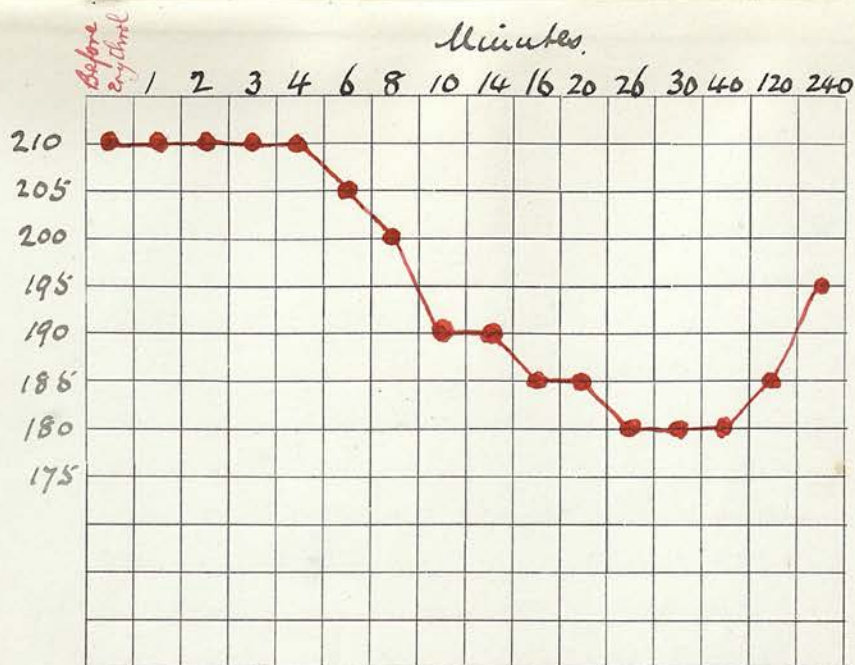
1 Grain Erythrol nitrate

observation 5



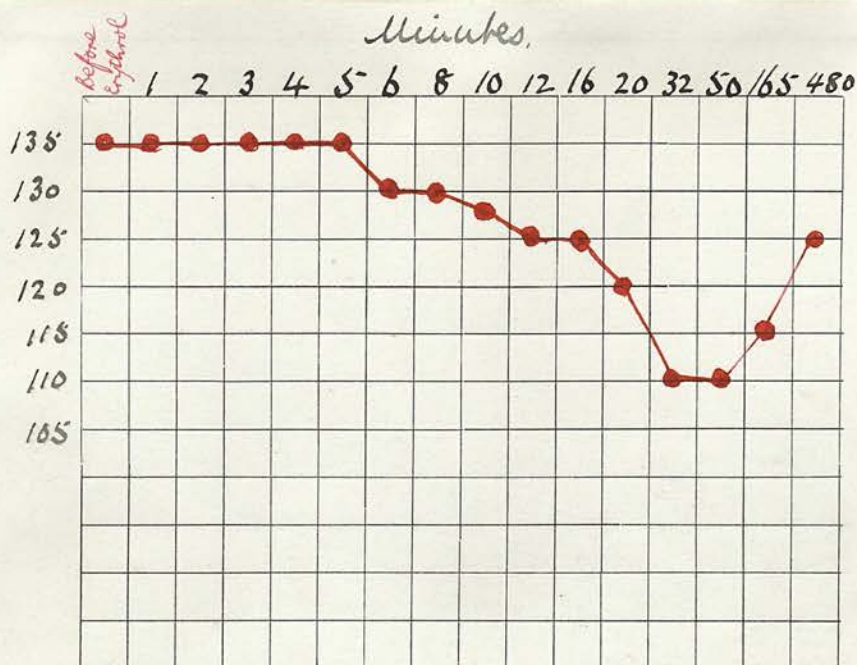
1 Grain Erythrol nitrate

observation 6



1 grain erythrol nitrate

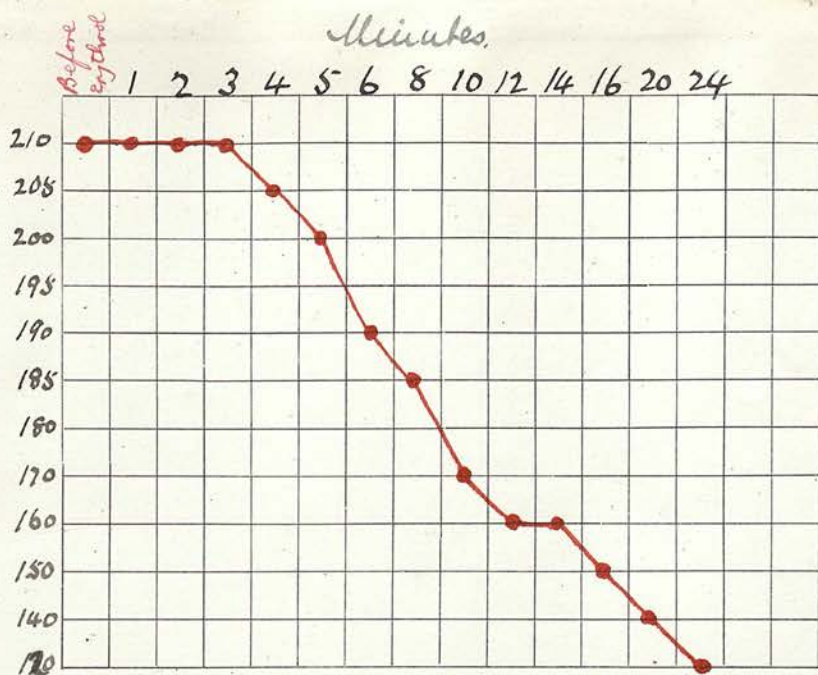
observation 7



1/2 grain Erythrol nitrate

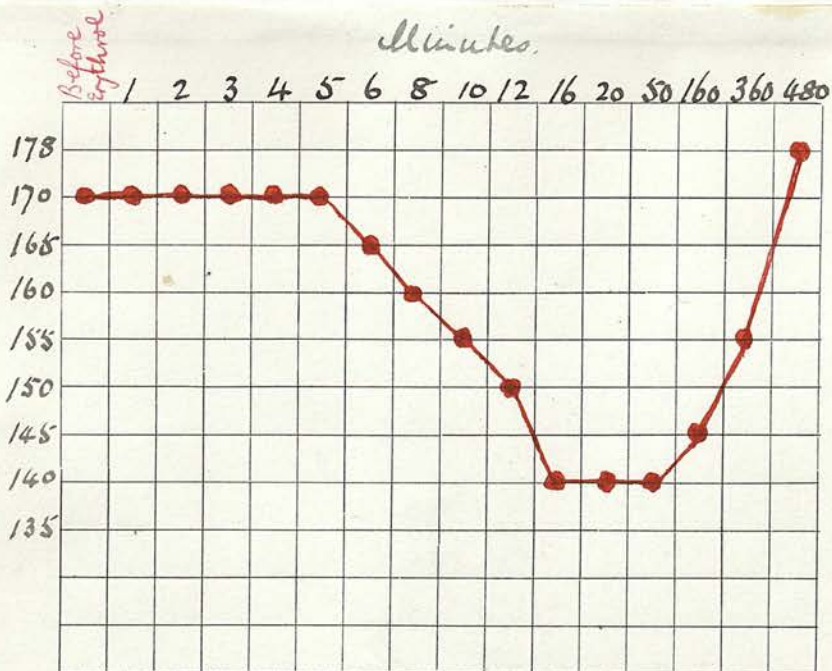
observation 8





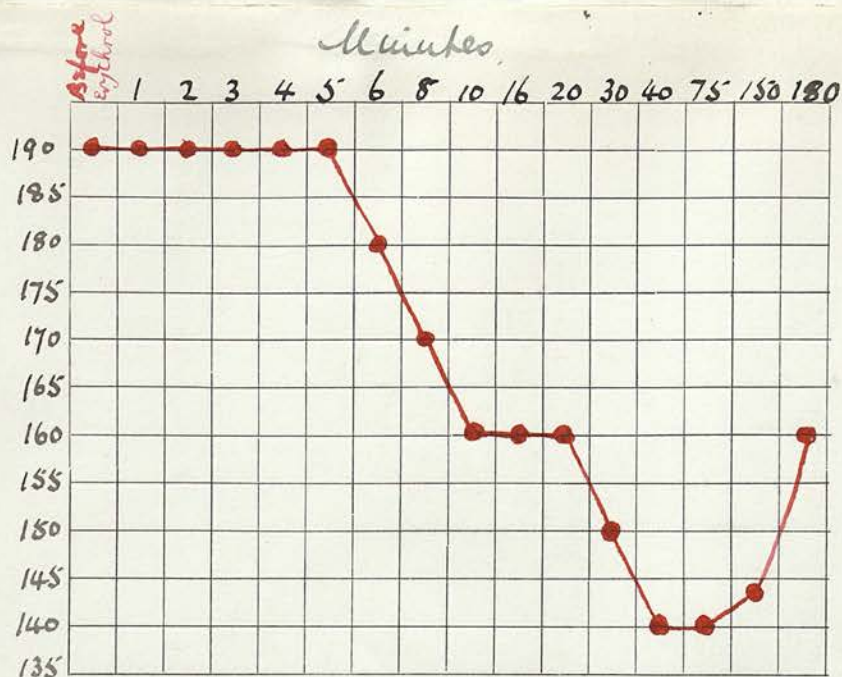
1 Grain Erythrol nitrate

Observation 9.



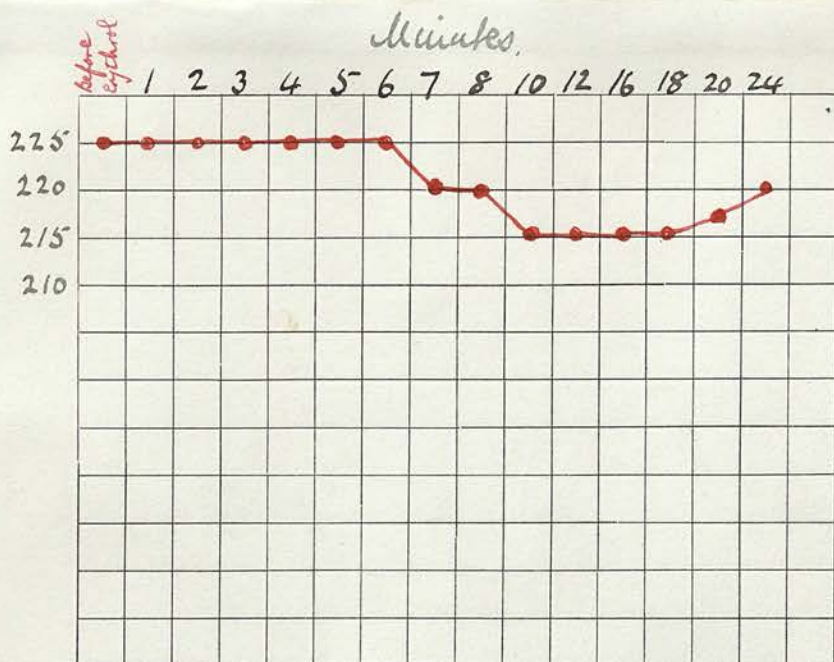
1 Grain Erythrol nitrate

Observation 10.



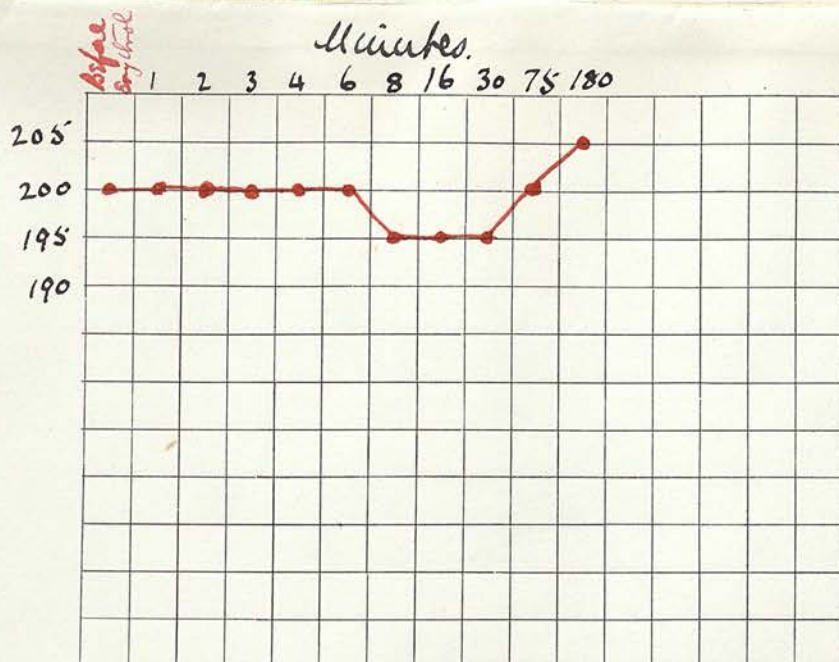
$\frac{1}{2}$  grain Erythrol nitrate

observation 11.



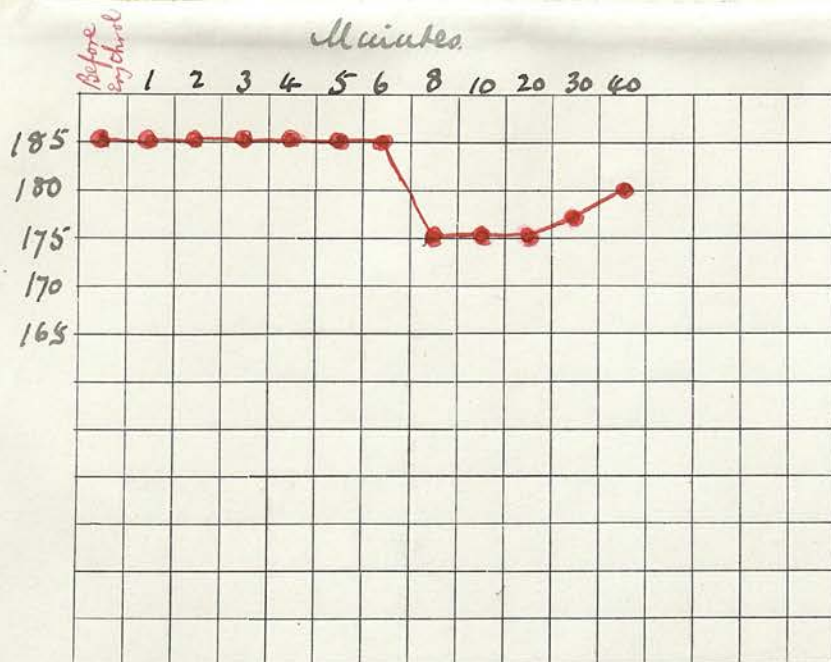
$\frac{1}{2}$  grain Erythrol nitrate

observation 12.



1 grain Erythrol nitrate

observation 13.



1/2 grain Erythrol nitrate.

observation 14.



47 a.

1. TIME IN WHICH THE PRESSURE BEGINS  
TO FALL.

Observation 1 in 4 minutes.

"	2	"	6	"
"	3	"	4	"
"	4	"	5	"
"	5	"	6	"
"	6	"	4	"
"	7	"	6	"
"	8	"	6	"
"	9	"	4	"
"	10	"	6	"
"	11	"	6	"
"	12	"	7	"
"	13	"	8	"
"	14	"	8	"

Over/

Over the 14 observations the pressure begins to fall in times varying from 4 to 8 minutes with an average of 5.7 minutes. Following the initial reduction the fall is one of about 5 m.m. of Hg. every two minutes until a maximum is reached.

2. MAXIMUM AMOUNT OF FALL PRODUCED.

Observation	1	25 m.m. of Mercury			
"	2	45	"	"	"
"	3	40	"	"	"
"	4	20	"	"	"
"	5	45	"	"	"
"	6	30	"	"	"
"	7	30	"	"	"
"	8	25	"	"	"
"	9	Indefinite, greater than 80.			
"	10	30 m.m. of Hg.			
"	11	50	"	"	"
"	12	10	"	"	"
"	13	5	"	"	"
"	14	10	"	"	"

Observation 12, 13, 14 showed little response to the nitrite. They are examples of cases that do not respond to nitrites.

Observation 9 was one where disastrous results followed, /



followed, and is an example of the danger of too severe an action. I will detail this case later. The average fall over the other ten observations was 34 m.m. of mercury.

### 3. TIME IN WHICH THE MAXIMUM FALL IS REACHED.

Observation 1 in 16 minutes.

"	2	"	14	"
"	3	"	14	"
"	4	"	24	"
"	5	"	20	"
"	6	"	16	"
"	7	"	20	"
"	8	"	32	"
"	9	not estimable		
"	10	"	16 minutes.	
"	11	"	40	"
"	12	"	10	"
"	13	"	8	"
"	14	"	8	"

Excluding 12, 13, and 14 (not suitable cases) and no 9, the average of the other 10 is nearly 22 minutes. Bradbury in observations on animals and also from sphygmographic tracings in man did not find the fall in/

in pressure to set in so quickly as I found it with the haemomanometer. He found the fall a very gradual one (e.g.) in one instance the pressure had fallen 22 m.m. **after 28 minutes** and it was only after 2 hours 48 minutes that the lowest level was reached - a fall of 40 m.m. of Hg.

I cannot agree with Bradbury that the fall is of this slow character. In my observations I never ~~had~~ failed to find a change of pressure in the first 10 minutes and moreover a maximum was attained in a comparatively short time - 22 minutes.

Observation 9 bears out these points well. Here already ~~is~~ 22 minutes as I will show, too great a fall was produced with collapse of the patient.

Whether the administration of the drug, in my observations, on an empty stomach and in a very soluble form is sufficient to account for the difference in our results I cannot say. Most of my observations were already made before I had read Bradbury's investigations. But on repeating my own and continuing them I was always able to obtain a quick initial fall and a maximum reached in a comparatively short time.

Though the total effect is *quickly* produced it does not pass off with an equal celerity as 4 and 5 will show.

4. TIME AFTER WHICH PRESSURE BEGINS TO RISE.

Observation	1	not observed.		
"	2	in	60	minutes.
"	3	"	95	"
"	4	"	95	"
"	5	"	70	"
"	6	"	60	"
"	7	"	100	"
"	8	"	120	"
"	9	not estimable		
"	10	"	100	minutes
"	11	"	120	"
"	12	}	Erythrol had little action.	
"	13			
"	14			

It will be observed from these figures that the maximum effect is maintained over a considerable period varying between 60 and 120 minutes or 1 and 2 hours. The whole 35 m.m. of Hg. reduction is maintained during this time.

Up to  $\frac{1}{2}$  hour the pressure was taken every two minutes then every 4 minutes up to an hour, afterwards at intervals of 10 to 15 minutes.

5. TIME IN WHICH THE PRESSURE REACHED ITS  
ORIGINAL LEVEL OR NEAR IT.

observation	1.	observed for 60 mins:	and pressure still at lowest level
"	2.	" " 70 "	and pressure had just begun to rise
"	3.	" " 115 "	and pressure had risen 5 m.m. from low
"	4.	" " 115 "	and pressure had risen 10 " " "
"	5.	" " 90 "	" " still 15 m.m. below origina
"	6.	" " 480 "	" " " 20 " " "
"	7.	" " 240 "	" " " 15 " " "
"	8.	" " 480 "	" " " 15 " " "
"	9.	not estimable.	
"	10.	observed for 480 "	" " " 5 " above "
"	11.	" " 180 "	" " " 30 " below "

In observations 1 and 2 I was able to take the pressure for periods of only 60 and 70 mins. In the others it will be observed that in the case of erythrol the rise towards the original pressure is very slow and in some cases 4, 6 and 8 hours elapsed before the complete effect of the single dose had passed off. My observations as regards points 4 and 5 agree with Bradbury's using the sphygmograph - that after a dose of  $\frac{1}{2}$  or 1 gr. erythrol tetranitrate the effect does not pass off till 5 or 6 hours have passed.

Summarising/

Summarising these results with erythrol nitrate

I find

1. The vasodilator action is evident in about 5 minutes.
2. The fall in pressure is a gradual one and the amount of reduction is about 35 m.m. of Hg.
3. The maximum effect is produced in about 22 minutes.
4. The maximum reduction is maintained for about 2 hours; the rise towards the original level is very gradual and the complete effect passes off in about 5 or 6 hours.

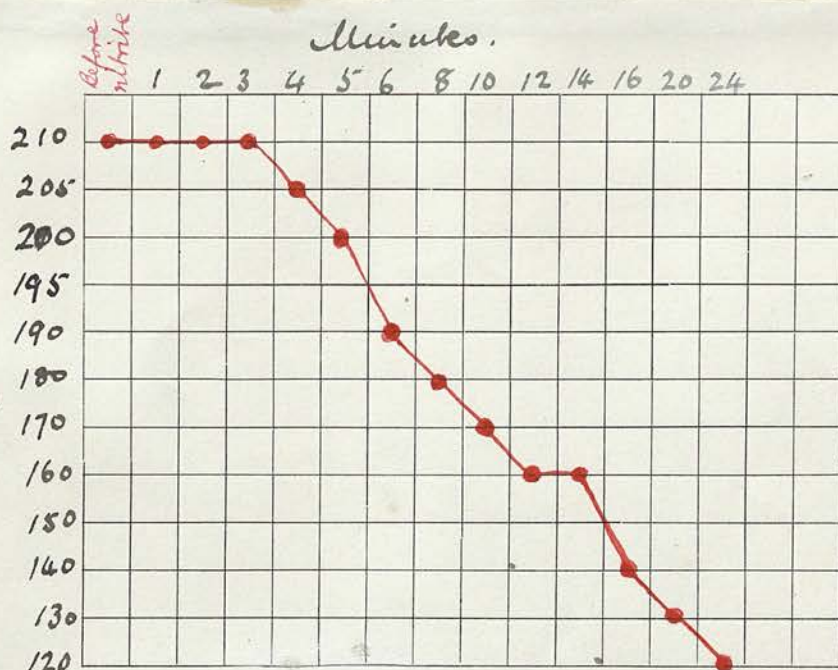
In observations 12, 13 and 14 erythrol nitrate produced little effect. There were cases corresponding to Nos. 2 and 5 with liquor trinitrini and No. 19 with sodium nitrite. One was a case of advanced cirrhotic Bright, the second also a cirrhotic Bright but not so advanced and the third a combined heart and kidney case with marked oedema.

Observation 9 I would refer to as an example of the dangers of overaction of erythrol nitrate. The patient suffered from Cirrhotic Brights in its earlier stages with a persistent high pressure of about 225 m.m. of Hg. with a tendency to periodic rises to over 250 m.m. His arterioles were still active and I found him readily respond to all the nitrites./



nitrites.

High pressure, per se, is in most cases where it exists conservative, compensatory, and necessary if the equilibrium that must exist between the various parts of the vascular system is to be maintained. Under these circumstances our aim should be to prevent this pressure rising higher, as it constantly tends to do, and at the same time we should remember, in producing a fall, that there is in every case a limit to reduction consistent with safety. If greater than a certain amount the reduction will only do harm. Observation 9 is a case in point, and I have observed other similar cases where this has been evident.



1 Grain Ergothol nitrate

Observation 9.

On the day of observation with erythrol nitrate the pressure was 210 m.m. 1 gr. was given.

He reacted very readily as the chart shows. The pressure began to fall in 4 minutes and thereafter fell about 5 m.m. every two minutes. When the pressure had reached 170 m.m. - in 10 minutes - he began to have unpleasant symptoms. He became pale, sweat broke out on him, he complained of feeling giddy, sick and faint. His pulse became slower. As the pressure continued steadily to fall the symptoms became aggravated and at the end of 25 minutes he fainted in bed. The last estimation of the pressure I was able to make was at the end of 24 minutes. It was then 120 m.m.

Here the erythrol had produced too great a vaso dilator action. The patient had bled into his abdominal veins. By stimulation and heavy pressure on the ~~abd~~omen he slowly became conscious but it was evening before he felt right and even then his pressure was very considerably below its normal level.

I would point out that, in this case, the symptoms set in when the pressure was still 170 m.m. - a figure considerably higher than would be expected in a healthy adult of his age, and even when he was in a state/

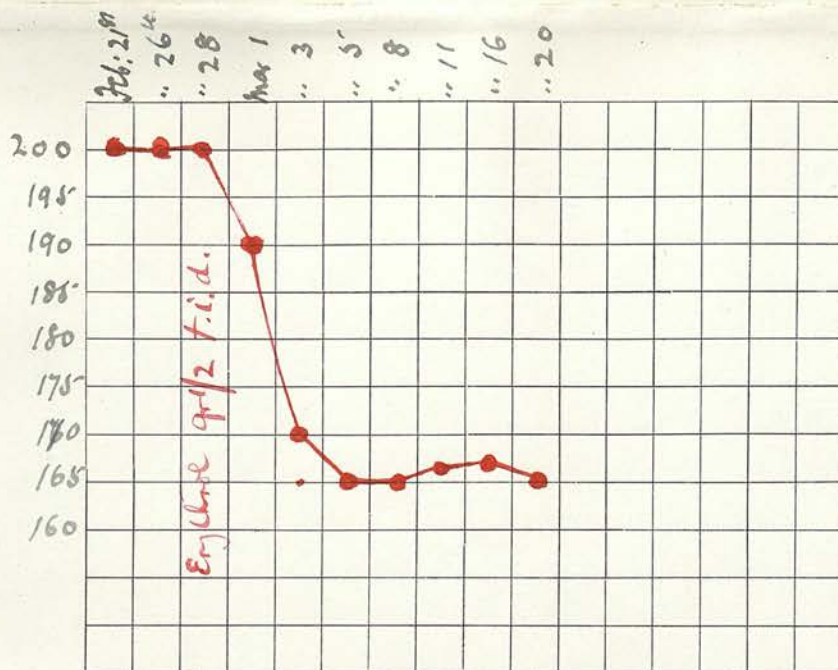
a state of collapse the pressure was still 125 m.m.  
 But his necessities demanded a much higher  
 ordinary working pressure for a vascular  
 equilibrium.

To a lesser extent I have observed the same  
 tendency in other cases viz. that it is dangerous  
 to produce by a nitrite too great an action. This  
 is of importance in relation to the dosage of  
 nitrites generally as I will show later.

#### ERYTHROL IN CONTINUED DOSES.

Erythrol in a single dose produces an action  
 lasting about six hours. It is reasonable to  
 suppose that if given two or three times a day one  
 would be able to maintain a reduction in pressure.  
 This I have tried in many suitable cases and always  
 successfully. The accompanying chart shows the  
 effect of  $\frac{1}{2}$  grain t.i.d. in a suitable case that  
 reacted well to a single dose. It was a case of  
 hypertension that had reached the stage where slight  
 arteriosclerosis had set in, though it was not  
*advanced.*





Erythrol nitrate  $\frac{1}{2}$  grain t.i.d. on Feby. 28<sup>th</sup>

He was put on a  $\frac{1}{2}$  gr. erythrol nitrate t.i.d. on February 21st. This was continued till March 20th and during this time the pressure was kept at 165 m.m. Previously it had been 200.

It is unnecessary to detail more similar cases.

#### DOSAGE OF ERYTHROL EMPLOYED.

My observations were made with  $\frac{1}{2}$  gr. and 1 grain tablets. I was not able to observe any relation between the amount of reduction or the length of action and the amount given.

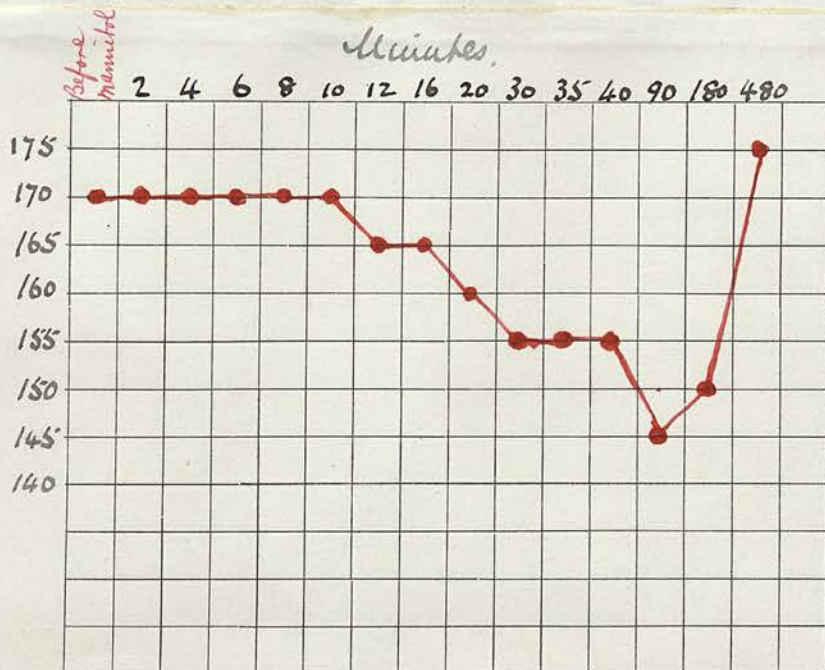
For example in observation 11,  $\frac{1}{2}$  grain was given. The fall was 50 m.m. and the pressure remained down for/

for over three hours. In observation three 1 grain was given. The pressure fell 40 m.m. and in 115 minutes had again begun to rise. I made observations too in the same case with both  $\frac{1}{2}$  gr. and 1 gr. and could not satisfy myself that the double dose produced a proportionally greater fall or lasted much longer.

The total result of the action in different individuals depends more, I take it, on the individual susceptibility and on the condition of the arterioles that are to dilate.

#### OBSERVATIONS WITH MANNITOL HEXANITRATE.

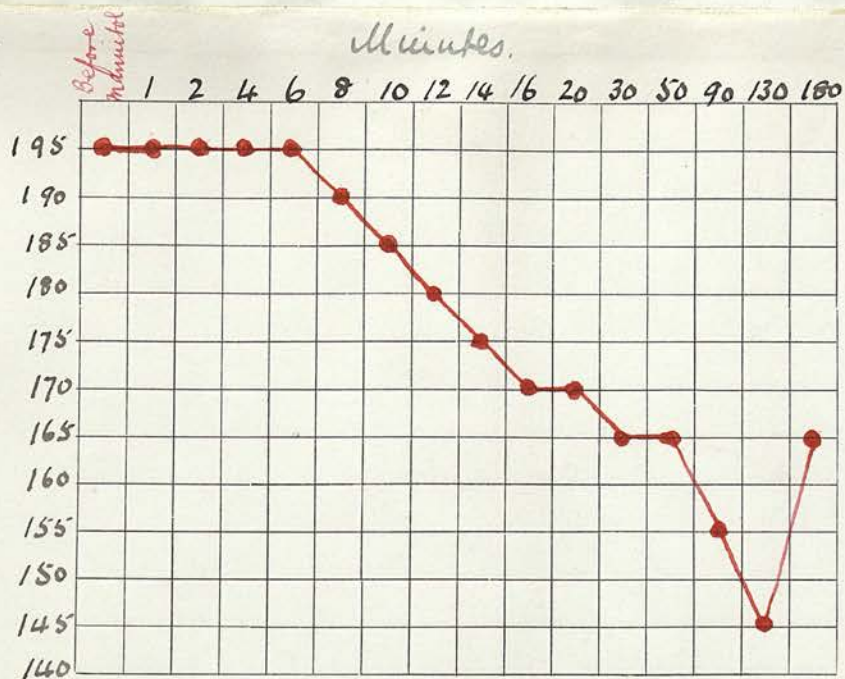
I made observations only with Martindale's chocolate tablets - 1 grain in each. I made eight observations in all and the accompanying charts show its action in the cases of high blood pressure in which I employed it.



1 Grain Mannitol hexate

observation 1.





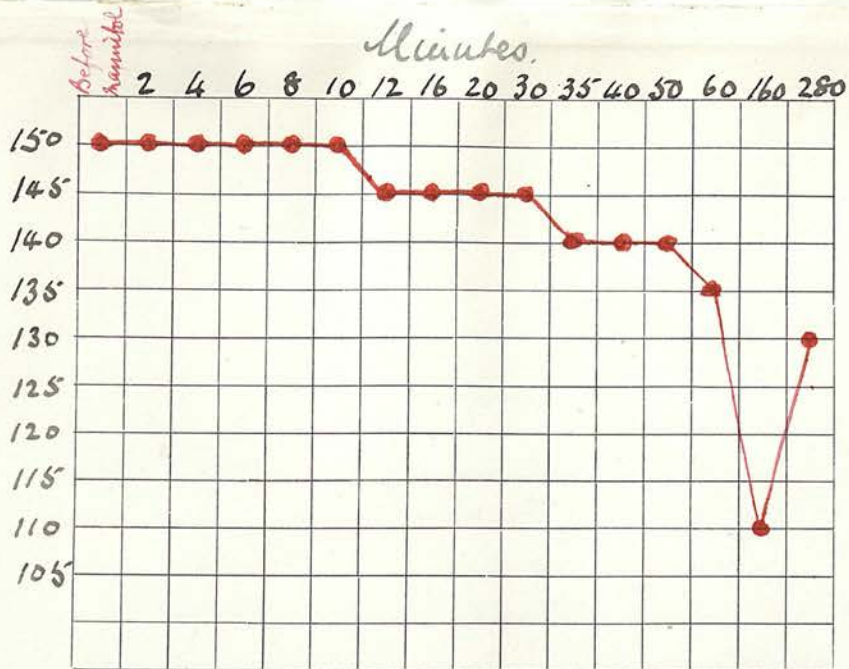
1 grain mannitol ritale

observation 2.



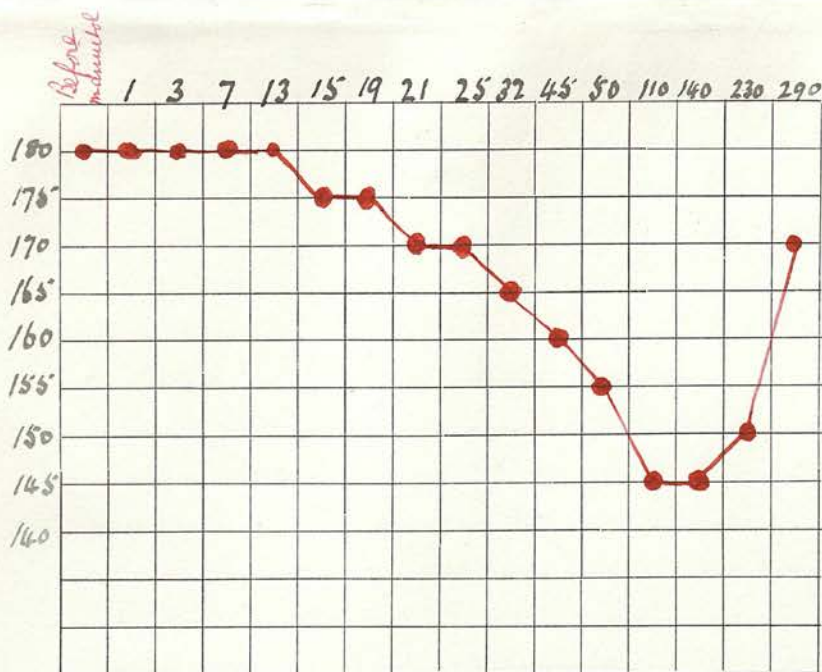
1 grain mannitol ritale

observation 3.



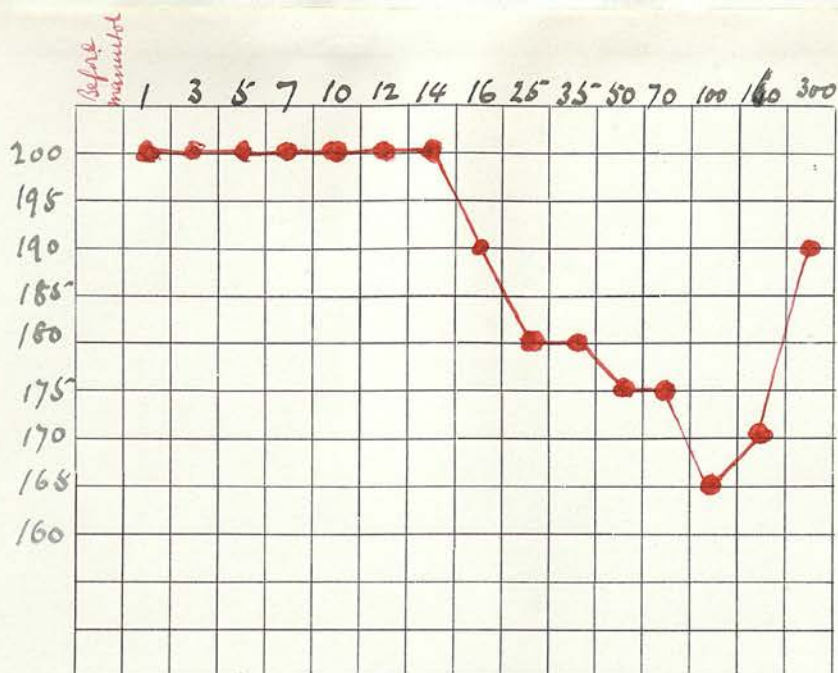
1 grain mannitol nitrate

observation 4



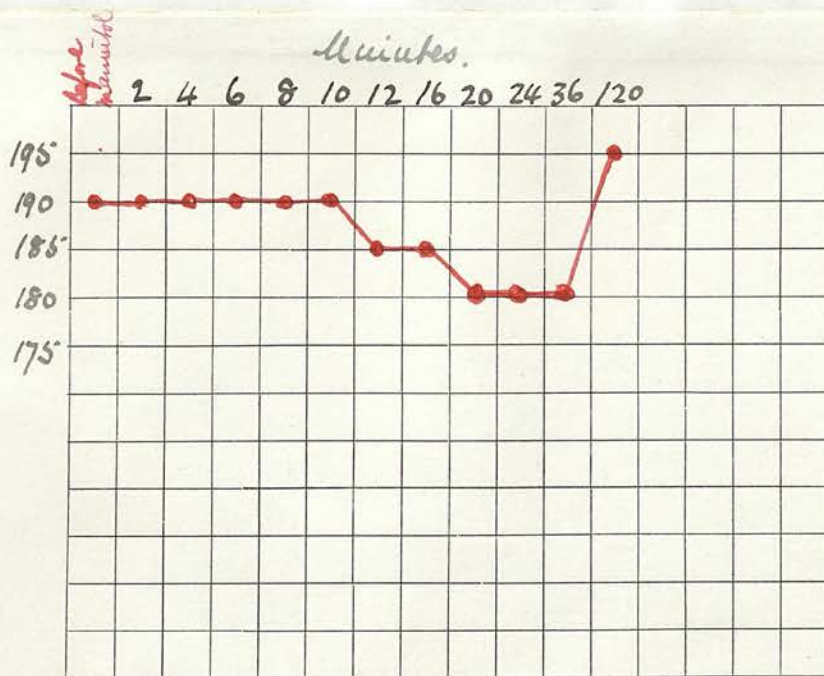
1 grain mannitol nitrate

observation 5



1 grain mannitol in water

Observation 6



1 grain mannitol nitrate

Observation 8.



1. TIME IN WHICH THE PRESSURE BEGINS TO FALL.

Observation 1. in 12 minutes.

"	2.	"	8	"
"	3.	"	10	"
"	4.	"	12	"
"	5.	"	15	"
"	6.	"	16	"
"	7.	no fall.		
"	8.	"	12 minutes.	

It will be observed that the initial fall of pressure is delayed much longer with Mannitol than with the other nitrites, the average time being about double what I found with erythrol nitrate.

In observation 7 over a period of  $3\frac{1}{2}$  hours no effect was obtained by 1 grain mannitol. The pressure was about 220 m.m. I repeated this observation after a week but again obtained no action.

2. MAXIMUM AMOUNT OF FALL PRODUCED.

Observation 1. in 25 m.m.

"	2.	50	"
"	3.	25	"
"	4.	45	"
"	5.	35	"
"	6.	35	"
"	7.	no fall	
"	8.	10 m.m.	

The amount of fall is about equal to that with erythrol. In 7 no fall was obtained and in 8 only a fall of 10 m.m. These, though high pressure was present, are examples of cases where a nitrite fails to produce its vasomotor action.

The average fall is 35 millimetres.

3. TIME IN WHICH THE MAXIMUM REDUCTION WAS  
ATTAINED.

Observation 1 in 90 minutes.

"	2	"	128	"
"	3	"	60	"
"	4	"	160	"
"	5	"	110	"
"	6	"	100	"
"	7		no fall.	
"	8	"	20 minutes.	

There is, as will be seen from these figures, a marked delay before the full effect of mannitol is produced. From the charts it will be seen that after initiation of action the fall is a much slower one than with erythrol and in no case has the maximum been reached in 22 minutes. I made observations with the two drugs in the same cases on several occasions and always observed the full effect in evidence much more quickly with erythrol than with mannitol.



4. TIME IN WHICH THE PRESSURE BEGINS TO RISE.

Observation 1	In	3 hours	
"	2	" 128 minutes	
"	3	" 140 "	
"	4	" 160 "	
"	5	" 180 "	
"	6	" 160 "	
"	7	no fall	
"	8	" 36 minutes.	

The maximum reduction is therefore maintained in suitable cases for from  $2\frac{1}{2}$  to 3 hours after which the effect begins to pass off but only slowly.

5. TIME IN WHICH THE ORIGINAL LEVEL OF PRESSURE OR NEAR IT IS AGAIN REACHED.

Observation 1. Between three and six hours.

"	2.	In 3 hours	pressure still	25 m.m.	below original			
"	3.	" $4\frac{1}{2}$ "	"	"	5 "	"	"	"
"	4.	" $4\frac{1}{2}$ "	"	"	25 "	"	"	"
"	5.	" 6 "	"	"	10 "	"	"	"
"	6.	" 5 "	"	"	10 "	"	"	"
"	7.	no fall						
"	8.	In $2\frac{1}{2}$ hours	10 m.m.	above original.				

The/

The effect of a single dose of mannitol does not pass off therefore ~~until~~<sup>have elapsed</sup> at 5 or 6 hours, a period corresponding to what ~~is~~ found with erythrol nitrate.

#### OBSERVATIONS 7 and 8.

In observation 7 no action was obtained and in No.8 very little. No.7 was a case of myocarditis with marked oedema and Cheyne Stokes breathing. In cases with cheyne stokes breathing one can follow beautifully by the haemomanometer the changes in pressure coincident with the changes in breathing. During the quiescent period the pressure is about 20 to 25 m.m. below what is found during the forced breathing, and in these cases it seems to me that the rise in pressure, arising as it does from a stimulation of the vaso motor centre, may be sufficient to prevent the vasodilator action of the nitrite. I observed the same in another case when given liquor trinitrini and erythrol tetranitrate.

#### OBSERVATIONS WITH COBALTO NITRITE OF POTASSIUM.

This nitrite has been introduced and employed in America. The argument for its use is as follows:- It is a more stable compound than Potassium nitrite and is less rapidly broken up in the system and its influence will therefore be more prolonged. It will not/

not at the same time act so vigorously or so suddenly as nitro-glycerine or Potassium nitrite and will be clinically more advantageous.

In observations with it I chose suitable cases where I had previously obtained positive results with sodium and Potassium nitrite and with erythrol but the results were negative.

It is a yellowish powder only slightly soluble in water.

Observation 1. 1 gr. No fall in pressure in 30 mins.

"	2. $\frac{1}{2}$ gr.	No	"	"	"	"	70	"
"	3. $\frac{1}{2}$ gr.	No	"	"	"	"	40	"
"	4. 1 gr.	No	"	"	"	"	40	"

So that up to 70 minutes I obtained no vaso dilator effect.

The idea underlying its introduction was essentially sound, but the necessity for its use is not now manifest in light of the fact that its intended purpose will be better achieved by erythrol and mannitol nitrates.

Observations with Liquor ethyl nitrit<sup>is</sup> (solution of ethyl nitrate). I made four observations with this nitrite but as vaso dilator action did not result I did not continue them.

Observation 1	20 minims	- no fall in pressure in 10 minutes
" 2	40	" " " " " 15 "
" 3	30	" " " " " 20 "
" 4	40	" " " " " 20 "

CONCLUSIONS.

From my observations with these various nitrites and nitrates certain conclusions may be drawn

1 in regard to their general action

2 in regard to their comparative action and utility.

1. GENERAL ACTION OF NITRITES.

a. nitroglycerine or liquor trinitrini, sodium nitrite, Potassium nitrite, erythrol, tetra-nitrate and mannitol hexanitrate are all powerful vaso dilators.

Cobalto nitrite of Potassium and liquor ethyl nitrit~~is~~<sup>is</sup> have ~~no~~ vaso dilator action. P

b. By blood pressure estimations ~~we~~ can ascertain as regards their action;

1. The time in which they act.
2. The amount of fall in pressure they produce.
3. The time in which the~~re~~ fall is produced
4. The length of time the vaso dilator action lasts.

These points are all of clinical importance ~~no~~<sup>no. 4</sup> being of special therapeutic value.

c. Nitrites produce a fall in pressure only in certain cases of hypertension. In others they produce no action.

Comparative/

Comparative action of the various nitrites.

Between the nitrites that are powerful vaso dilators in suitable cases of high blood pressure, there are differences in the results that demand attention.

(Amyl nitrite I did not make observations with as its action is so speedy and sudden as not to be easily ascertained by the blood pressure methods I employed. Graphic records of blood pressure are necessary for amyl nitrite).

These differences I would draw attention to under the different analytic headings.

1. THE TIME IN WHICH THE PRESSURE BEGINS TO FALL.

The order of their action is the order in which I have described them viz.

1. Nitroglycerine or liquor trinitrini - 1 minute
2. Sodium and Potassium nitrites - 5 minutes.
3. Erythrol nitrate - about  $5\frac{1}{2}$  minutes.
4. Mannitol nitrate - about 10 minutes.

All produce an action within 10 minutes after administration.

2. AMOUNT OF FALL IN PRESSURE IN MILLIMETRES OF MERCURY.

The average amounts of fall in my observations were:-

liquor/



liquor trinitrini	- 28 millimetres
Sodium and Pot. nitrites	- 32.5 millimetres
Erythrol nitrate	- 34 millimetres.
Mannitol	- <b>35</b> "

Between the least and the greatest there was only a difference of 6 millimetres a figure that might probably be reduced over more extensive observations.

### 3. TIME IN WHICH THE MAXIMUM AMOUNT OF FALL IS OBSERVED.

In the four nitrites the average time was:-

1. Liquor Trinitrini -  $4\frac{1}{2}$  minutes.
2. Sodium and Potassium nitrites - 14 minutes.
3. Erythrol nitrate - 22 minutes.
4. Mannitol nitrate - almost 100 minutes.

Though the amount of fall as seen under 2 is very nearly equal in all, there is a marked difference in its mode of production.

It was seen under 1. that these nitrites begin to act in 1, 5,  $5\frac{1}{2}$  and 10 minutes; the maximum therefore is produced in  $3\frac{1}{2}$ , 9,  $16\frac{1}{2}$  and 90 minutes, after the vaso dilator action begins. During these various times we have with each a fall of say about 30 ~~millimetres~~ and therefore with liquor trinitrini a very sudden and prompt action, not so sudden in the case/

case of sodium and potassium nitrites, more prolonged but not so much, with erythrol nitrate - and lastly a very gradual and slow action with mannitol nitrate.

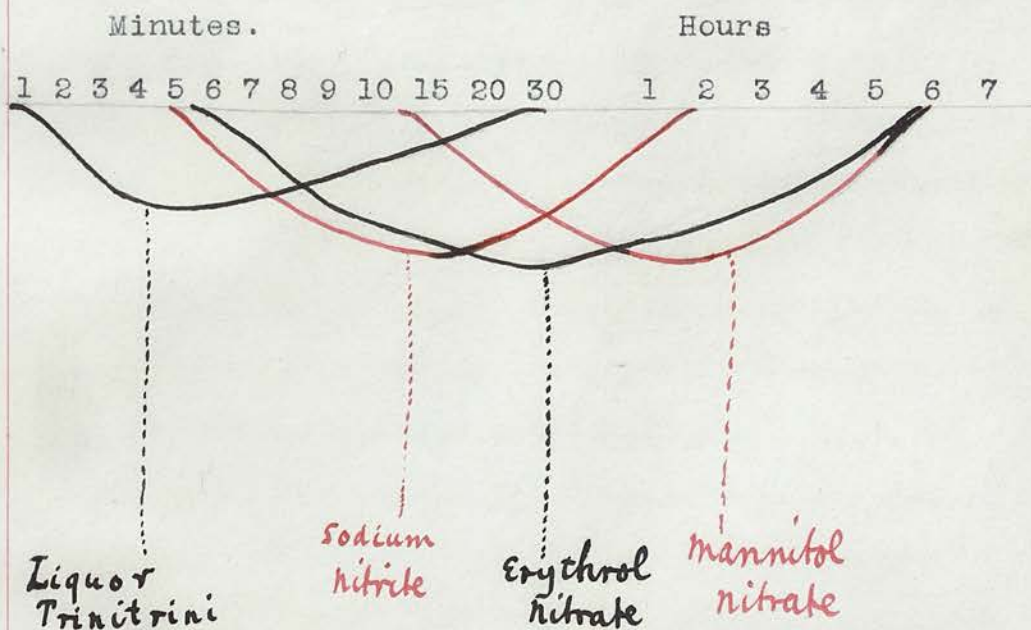
#### 4 and 5. THE RISE IN PRESSURE AFTER THE FALL.

Variation in action between the different nitrites becomes still more evident when one studies the rise in pressure towards its original level.

1. With liquor trinitrini there is no tendency for the pressure to remain at the level of maximum fall. It begins almost immediately to rise again. The rise is certainly somewhat slower than the fall, but in all cases the original level is again reached within 30 minutes after its administration.
2. Sodium and Potassium nitrites have a more extended action. A maximum fall is reached in about 10 minutes but unlike trinitrini this is maintained for periods varying between 25 and 50 minutes. Then the rise of pressure is only gradual and the original level is not reached until two hours have passed.
3. Erythrol and Mannitol nitrates behave alike as regards length of action. The maximum action is maintained for between two and three hours - a much longer time than with sodium nitrite. When the rise/

rise in pressure sets in, it is very gradual and the original level is reached only after 5 or 6 hours. The length of time of action of these various nitrites lies between 30 minutes and six hours, a fact that enables us to select the requisite nitrite in any particular case.

The various points determined for these nitrites in my investigations are well seen in the following diagram (after Bradbury).



The curved lines of the four nitrites give a comparative idea of the various points I have endeavoured to ascertain. viz: - when the action of the nitrite begins, when the maximum reduction is reached, and when the action entirely passes off. For example, with liquor trinitrini the action begins in one minute, a maximum is attained in 5 minutes and the whole action passes off in 30 minutes.

DOSAGE OF THE THERAPEUTIC NITRITES.

In combating conditions of elevated blood pressure it is important that a suitable dosage of these active nitrites should be scientifically arrived at.

It has to be recognised that in all cases, though within limits, hypertension is not necessarily harmful to the individual, and the idea that it has to be always attacked by every means in our power has just sufficient truth to be a serious misconception. When found, it is to be looked on primarily as a compensatory change, and the whole condition of the individual thoroughly investigated before it is condemned, and attempts made to reduce it.

Just as a left ventricle in aortic incompetence has to hypertrophy to accom<sup>m</sup>odate itself to the altered conditions due to the aortic leak, so high blood pressure must be similarly considered compensatory if the proper relationship is to be maintained (a) between the various parts of the circulation and (b) between/



between the circulation and the tissue *wants*. Undoubtedly we find, in every case that is followed for some time, that, once started, the tendency is for the blood pressure to progressively increase, and in time a stage is reached when it becomes absolutely necessary for the patients well-being to step in and actively interfere.

And by the use of nitrites we can do a great deal in a number of hypertension cases. It must be remembered, however, that our aim must not be to reduce the pressure to what we consider a normal level for that individual, but only to effect such a reduction as shall alleviate symptoms and prevent the increased strain that is being thrown on the heart and blood vessels by the high pressure. That too great a reduction may be harmful I have pointed out in such cases as observation 9 with erythrol nitrate, where unpleasant symptoms were induced by too great reduction, and that too at a point in the pressure still markedly too high for a normal standard, but too low for the particular individual's vascular economy.

From the observations I have detailed and many others, I made an attempt to ascertain what reduction of pressure is both necessary and safe for relieving and alleviating symptoms and in maintaining/



maintaining the pressure at a level that shall be innocuous to the patient. I made observations in many cases with hypertension when symptoms had developed such as pain, headaches, giddiness, bleeding at nose, condition of the stomach, and heart, etc., that could be traced to the elevated pressure.

From my observations with the haemomanometer I invariably found that such symptoms were alleviated or disappeared altogether with a reduction of pressure amounting to about 30 millimetres of mercury, and that if this amount of fall could be maintained the symptoms did not reappear and the individual's general condition improved.

I then made observations with the active nitrites in varying amounts to ascertain the quantity of each that would produce as near as possible such a reduction.

It was after and on account of these investigations that I adopted the doses I employed in the detailed observations with the various nitrites.

#### 1. Liquor trinitrini.

Where a single dose - to be repeated if necessary at  $\frac{1}{2}$  hourly intervals - is prescribed I would recommend 2 minims as the one likely to be most beneficial in hypertension.

If/

If necessary this amount may be increased rapidly but only for a short time owing to the tolerance that is acquired in a great many cases.

## 2. Sodium and Potassium Nitrite.

In suitable nitrite cases, 2 grains produces a reduction of over 30 millimetres of mercury. This action will last two hours and only after this time is it necessary to repeat it. No benefit is obtained by increasing the dose.

## 3. Erythrol nitrate.

With this drug a dose  $\frac{1}{2}$  to 1 grain will produce the beneficial reduction and its effect will last about 6 hours. I would recommend the use of the smaller dose as from my observations I came to the conclusion that in some cases there was a marked susceptibility to the drug and in them the 1 grain dose might do harm. This can easily be ascertained however, by making an observation on the individual with the haemamamometer.

## 4. Mannitol nitrate.

I have used only tablets of 1 grain. These have always answered the purpose and I have not observed the same susceptibility or any tendency to unpleasant effects with it, probably owing to the fact/

fact that it produces its maximum effect much more slowly than erythrol does.

I would point out, however, that in all cases the useful and suitable dose for each individual can readily be ascertained by making a preliminary observation or two, and noting the effect of the nitrite in regard to the amount of action and the time it lasts. If this plan be followed the nitrites will be necessarily more under control and therefore the more likely to be beneficial.

#### THE USES OF NITRITES IN ELEVATED BLOOD PRESSURE.

From the mode and manner of action it is to be expected that these nitrites will be serviceable in conditions of high blood pressure.

I do not claim for them a curative action. This will only be obtained in hypertension when we have learned more of the cause underlying it and of its production and progression.

In the meantime, however, anything that will serve as a check and relief to the increasing hypertension is the best weapon we have at our disposal, and the nitrites through their vaso dilator action will undoubtedly help.

From the observations I have made one may to a certain extent deduce the conditions under which their usefulness will be brought out.

LIMITATIONS OF THE NITRITES.

Their limitations too, one was able to elucidate during the investigation and it will be convenient to summarise these first of all.

As will have been noticed I have included under each of the various nitrites observations where a negative result was obtained. These are Nos. 11 and 12 under liquor trinitrini, No. 19 under Sodium and Potassium nitrite, Nos. 12, 13 and 14 with erythrol nitrate, and Nos. 7 and 8 under mannitol nitrate.

These observations represent six cases in whom no or little vaso dilator effect followed the administration of a nitrite. Two were cases of advanced cirrhotic Brights, one an advanced inflammatory Bright, one a case of combined mitral heart and generalised arteriosclerosis, one a generalised arteriosclerosis, and the 6th a combined heart and kidney case with marked cedema. In all the pressure was high - over 200 millimetres, - with a tendency to irregular temporary rises.

Arteriosclerosis as I have pointed out only produces marked elevation of blood pressure when it has involved certain large areas of capillary and arteriole distribution, and more particularly if the splanchnic area has become involved. In the clinical/

clinical cases I have mentioned except the last, the process of sclerosis had not only already set in but become advanced in these areas and it naturally follows that the power to dilate under nervous influences or after administration of a nitrite has been partially or completely lost. The arterioles have become firm, hardened and non elastic and their power of dilatation gone. In these conditions therefore the nitrites are contra-indicated. For no dilatation will result and it may be harm will follow their administration as I pointed out in observation 11 under liquor trinitrini.

#### NITRITES IN PROGNOSIS.

So far as treatment is concerned then in these clinical conditions I have mentioned, the nitrites will be unavailing. At the same time I would point out a use to which they may be put in these sclerotic cases. They are useful from a prognostic point of view. In all cases of Bright's disease and in conditions where generalised arterio sclerosis is suspected help will be got from the use of a nitrite in ascertaining to what stage the condition has advanced and what is the hope for the future. In the early stages of cirrhotic Brights, chronic inflammatory/



inflammatory Brights and the presclerotic stages of hypertension, I have found always respond readily to any of the nitrites. As the conditions advance and sclerosis sets in the response becomes less and less marked until one obtains no or little action as in the cases I have detailed under the various nitrites.

When in any of these conditions the nitrite produces no vaso dilator action the prognosis is a bad one.

If on the other hand we still obtain a fall of from 25 to 30 millimetres of mercury from a single dose of say 2 minims liquor trinitrini or  $\frac{1}{2}$  grain of erythrol we can say that the condition is still in its early stages.

In these cases I would strongly recommend this plan of administration of a nitrite as a help in prognosis.

#### NITRITES IN OEDEMA.

Case No.6. Heart and kidney with marked oedema. In cases of high pressure there comes a time through its progressive increase, when the heart is unable to overcome the resistance and more particularly so if in addition one of the valves be affected. The ordinary symptoms of failing heart then set in - breathlessness, oedema of legs and abdomen etc. In these cases so long as the oedema continues marked I have found/

I have found nitrites quite inactive in producing dilatation of the arterioles even though the pressure remain high.

If the individual respond to other treatment and the oedema is got rid ~~of~~ then nitrites are of service along with heart stimulants and their vaso dilator action is again evident. This I observed - several times in my investigations e.g. observation No.14 with erythrol. This patient had reacted well to all the nitrites before oedema set in. Once it became marked, no response was obtained with sodium nitrite and erythrol, but on its disappearance their action again became established.

It may be in those cases that the oedema acts as a mechanical hindrance to the dilatation of the arterioles.

I would from my observations therefore suggest that we do not in the following conditions of hypertension obtain a response to nitrites, and their use is contraindicated.

1. Cirrhotic Bright's disease when advanced.
2. Chronic Inflammatory Bright's disease when advanced.
3. In cases with generalised arterio sclerosis without independent signs of kidney involvement.
4. Heart cases with large amount of oedema with high blood pressure.

CONDITIONS OF HIGH BLOOD PRESSURE IN WHICH  
NITRITES ARE OF USE.

The use of nitrites in treatment has been limited hitherto to a great extent by the knowledge of the suddenness and rapidity of their action. This undoubtedly holds good for amyl nitrite and nitro-glycerine or liquor trinitrini, but as I have definitely shown we may expect a much less sudden and more prolonged action and of equal amount from sodium and potassium nitrites and erythrol and mannitol nitrates. At the same time, therefore, each of the nitrites has its own particular field of action and all are of service.

1. Liquor trinitrini or nitro-glycerine.

In hypertension amyl nitrite and nitro-glycerine will have their sphere of action particularly in those cases where the speedy relief of painful symptoms is desired. It is well known that in high blood pressure aggravation of symptoms and onset of fresh symptoms are produced by the tendency in these cases for temporary and periodic elevations to set in. These in all probability result from a condition of temporary spasm in the arterioles, and pains, headaches, giddiness, breathlessness, epistaxis etc. follow. Here with liquor trinitrini, owing to its prompt action -/

action - within 60 seconds - we can relieve the condition of spasm and reduce the blood pressure to its accustomed level.

A dose of two minims repeated at intervals of half an hour or slightly less will relieve the patient. On the other hand with liquor trinitrini as I have shown we cannot expect any permanent reduction of the blood pressure and for use over a period it should not be employed.

Brunton has recommended <sup>that</sup> nitro-glycerine should be given in repeated and divided doses through the day and thus we should be able to keep the tension low. I have repeatedly attempted this in suitable cases of hypertension but always without success. For this purpose we should always use one of the longer acting nitrites.

#### Uses of the longer acting nitrites.

(Sodium and Potassium nitrite: erythrol and mannitol nitrates).

I pointed out when discussing conditions of high blood pressure, that the most important group of hypertension cases from a therapeutic standpoint - is what I have called the presclerosis cases. These, as I said, gradually and surely lead to generalised sclerosis if entirely untreated and exist long before a palpable sclerosis is evident.

In/

In the early stages these cases are very amenable to treatment, and a great deal may be done for them by attention to diet, drink, exercise, by hydrotherapy etc. And it is in these cases too that the longer acting nitrites are a most useful addition to other treatment. In these cases owing to the high pressure we have a constant overstretching of the vessels, in addition to their being constantly bathed by a toxic fluid. Any means that will assist in a remission of this stretching to which the vessels are subjected will be a valuable aid to other treatment. By dilatation of the arterioles we ensure in addition a free discharge through the capillaries still patent and save the arteries behind them, and so help to stave off the permanent changes in the vessels that are bound to follow. This dilatation we can effect by the use of sodium and potassium nitrites and more beneficially by erythrol and mannitol nitrates. Even a single dose by reducing the pressure for a period of six hours has benefited, not only the arterioles and arteries but the heart, and the maintenance of a moderate reduction will be still more useful. I have found the longer acting nitrites of immense value in these early conditions of hypertension not only in relieving symptoms but in improving the general condition/



condition of the patient, in addition to preventing the continuous strain on the vessels themselves. It is not necessary to persist with the nitrite continuously I have found that a course of it for a month, followed by cessation for a month, and then renewal for another period suits best.

Though giving the best results in the early stages of high blood pressure erythrol and mannitol nitrates are also of some service after we know that the sclerosis has set in. In the early stages of cirrhotic Bright's and of chronic inflammatory Bright's and in the hypertension cases after sclerosis has become evident they are still of service and will continue to be so as long as the individual's vessels dilate. In these cases too these nitrites save and preserve the arteries and the heart, and help to check the fatal advance.

The longer acting nitrites I would recommend as serviceable in the following conditions of high pressure.

1. Temporary elevations of blood pressure from whatsoever cause, either in cases where the pressure was high to start with or temporary rises found as concomitants in many diseased conditions.
2. They are of most service in the important cases of hypertension before sclerosis has set in or is slight./

slight.

3. In these same cases after sclerosis has set in if not too advanced.

4. In cirrhotic Bright's Disease and in chronic inflammatory Bright's Disease if not too advanced, and also in uraemic attacks occurring in these conditions.

Between Sodium and Potassium nitrites on the one hand and erythrol and mannitol nitrates on the other the difference in these cases is entirely one of time.

#### OBSERVATIONS WITH OTHER SUBSTANCES.

I made numerous observations with other substances to test their vaso dilator effect, as they have been recommended and used in hypertension conditions. These investigations I made in the same cases where I had previously found a response to the various nitrites.

Among them were Potassium Iodide, Ammonium Benzoate, Ammonium hipporate, Diuretin and Thyroid extract.

##### 1. Potassium Iodide.

This drug has for many years been a chief standby in cases showing arteric sclerosis and clinically it is undoubtedly of great service. So far as one can judge however, from reading present medical/

medical literature it has fallen into disrepute - many observers denying any good from it in these conditions.

Zgorski declares that in cases with arterio sclerosis he has had no benefit from the iodine preparations. Frenkel of Berlin and Ludwig Wiel of Stuttgart and many others deny its practical use in hypertension. Others think it unsuitable in some cases but of great service in others.

Apart from its general utility numerous discussions have also taken place as to the action of the iodine preparations in vascular disease.

Many years ago Romberg gave it as his opinion that the action of Iodine and the Iodides was not on the blood vessels but on the blood. This view was not generally accepted. Huchard and others described Potassium Iodide as a vaso dilator and a depressor of arterial tension.

Later O. Muller professed to have shown that Potassium Iodide has nothing to do with blood pressure, and that it is useless where the disease producing the increased pressure has progressed to anatomical deformities, though it is of service when the condition is still one of deficient blood irrigation. He is of the opinion, and thus reverts to Romberg's view, that the iodine preparations act by/

by lowering the viscosity of the blood "as a whole."

I made observations with Potassium Iodide

1. in single doses.
2. in repeated doses over a period.

#### 1. SINGLE DOSES.

For the purpose I chose suitable cases where I had already found vaso dilatation from the use of the nitrites, and I gave <sup>the</sup> iodides under the same conditions as to time etc.

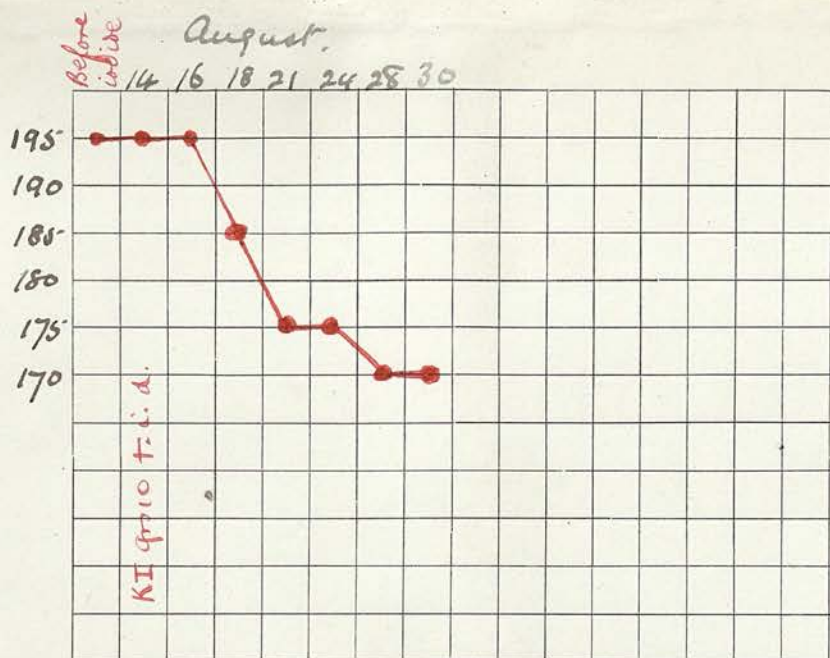
I used 10 and 15 grain doses and in none of my observations—eight in number - with a single dose was I able to observe a vaso dilator effect over periods up to 100 minutes.

#### 2. REPEATED DOSES.

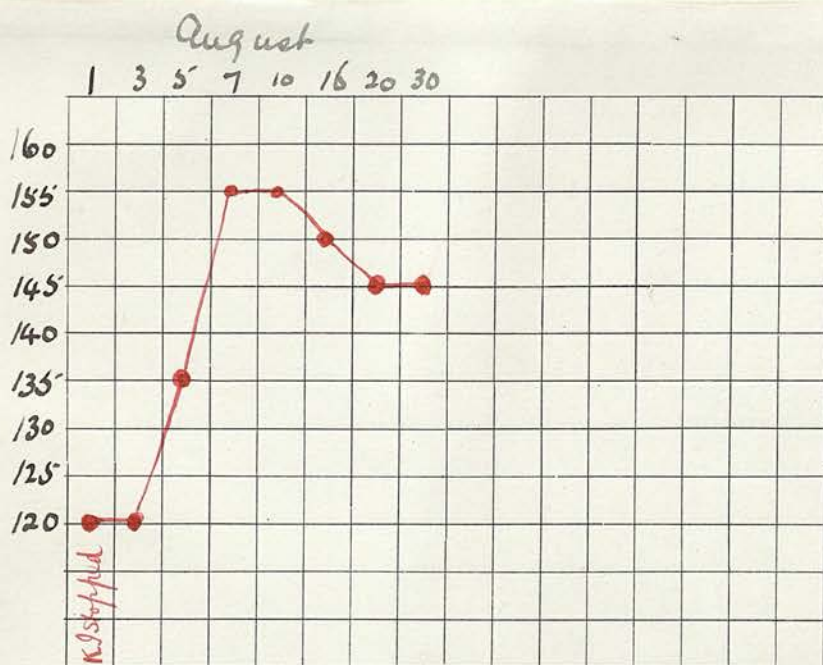
I made several observations with Potassium Iodide over a period. This I did in two ways

1. By observing a fall after patient had been on iodide for a time.
2. By observing the rise after the iodide had been stopped.

The accompanying charts show the results.



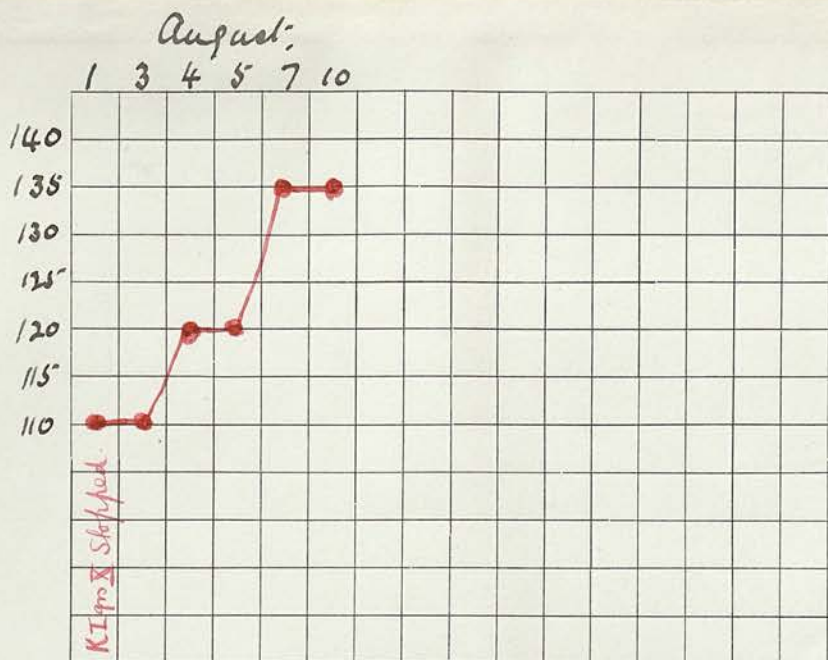
Potassium Iodide grs  $\Sigma$  t.i.d. Observation 1



Observation 2

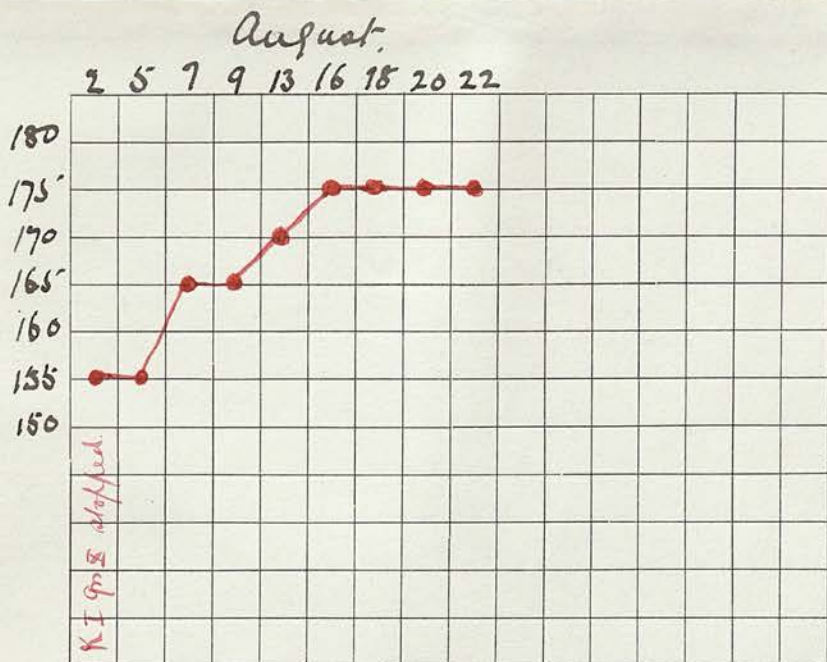
Potassium Iodide grs  $\Sigma$  t.i.d. for a month before August 1<sup>st</sup>. Iodide stopped on that date





Observation 3.

Potassium Iodide for month till August 1<sup>st</sup>. Iodide then stopped



Observation 4

Potassium Iodide gm & till for month till August 2<sup>nd</sup>. Iodide then stopped

## Observation 1.

Patient with pressure of 195 m.m.

Put on iodide on 14th August grs.X t.i.d.

In a fortnight the pressure had fallen to 170 m.m.

## Observations 2, 3 and 4.

In these cases the patients had been on iodide for a month, and I am unaware what the pressure was before its administration. From the charts it will be seen that following the cessation of the iodide there was a speedy rise in the pressure amounting to 35 m.m., 25 m.m., and 20 m.m. within a few days.

I do not wish to dogmatize from these few observations as I was chiefly concerned in ascertaining its vaso dilator action.

Further observations require to be made, but these serve to show that Potassium Iodide has, when continued over a period, an effect on the blood pressure.

From the fact that no action is obtained with a single dose it is unlikely that Potassium Iodide is a vaso dilator to any great extent; as has been suggested it may act by reducing the viscosity of the blood and this would naturally result in a lowered blood pressure.

I/

I made also numerous observations with ammonium benzoate and diuretin (for which a vaso dilator effect has likely been claimed) and thyroid extract.

With none of these drugs was I able to obtain a vaso dilator effect with increasing doses and over periods of observation up to two hours, and as I was unsuccessful I need not detail the observations. Given over a period too I did not find any reduction of pressure with diuretin or thyroid extract, though ammonium benzoate seemed to have a slight effect, but my observations over a period were too limited to draw any conclusions.

In my observations therefore on vaso dilators substances I found only liquor trinitrini, sodium and potassium nitrites, erythrol and mannitol nitrates active in single doses. The latter four are also beneficial in repeated doses in maintaining a reduction of blood pressure. Potassium Iodide though not a vaso dilator in a single dose has a marked effect in reducing blood pressure when given over a period of time. The other substances I found of no service in hypertension.

## REFERENCES

1. v.Basch Die Herzkrankheiten bei arteriosclerose  
Berlin 1901.
  2. Brunton Lancet 1906.
  3. Bradbury B.M.J. 1895.
  4. Clifford Allbutt B.M.J. Jany.1906.
  5. Clifford Allbutt Hospital 1907.
  6. Carter American Journal of Medical Science 1901.
  7. Hare Therapeutic Gazette 1905.
  8. Hasenfeld,Arthur Deutsch: Arch: f.klin: Med: 1897.
  9. Hirsch, Carl Deutsch: Arch: f.klin: Med: 1900.
  10. Herringham B.M.J. Jany 1907.
  11. Huchard Traite Cliniques des Maladies du coeur  
et des Vaisseaux 1893.
  12. Janeway The Clinical Study of Blood Pressure.
  13. Loomius Medical Record 1905.
  14. Leech B.M.J. 1893.
  15. Meigs. Human blood vessels.
  16. Oliver Lancet 1907.
  17. Oliver Studies in Blood Pressure 1901 and 1906.
  18. Russell Arterial Hypertonus, Sclerosis, and Blood  
Pressure.
  19. Zgorski Repertorium des Praktische Medizin 1904.
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